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## SOME HIGHLIGHTS OF THE EARLY HISTORY OF CHICAGO

J. R. LINDSAY

*Chicago Ill., U.S.A*

Some of you are well acquainted with America and the Chicago region from previous occasions but many of you are here for your first visit. We hope that you will all have pleasant and interesting time in the next few days we hope to show you some of the places of interest in Chicago and its surroundings. By way of introduction to this region I propose to review for you some of the highlights of Chicago's early development.

Early in the 16th century Jacques Cartier of France first explored the St. Lawrence River Valley and in 1534 reached the Lachine Rapids, at what is now Montreal. The French were interested mainly in fisheries and the fur trade. In the 16th and 17th centuries colonization of the North Carolina, Virginia and the Massachusetts Bay areas was developing but was limited to the east of the mountain until early in the 18th century. The Spanish had already arrived in Florida and had a small colony at St. Augustine.

In the 17th century colonization of "New France" under Champlain and Cardinal Richelieu was slowly progressing. Explorations continued westward to the upper end of Lakes Huron and Michigan eventually to extend down the Mississippi River to the Gulf of Mexico. French missions were established at St. Ignace near Mackinac Island and in 1666 on the shores of Lake Superior.

The first white men to set eyes on the site of future Chicago were a French-born Jesuit, Father Jacques Marquette and a Canadian explorer and map-maker Louis Joliet, with five canoe men or voyageurs in 1673. They were looking for the Mississippi River which they knew only by legend, thinking it might lead to the fabulous riches of the Orient. The route followed by them took them across Lake Michigan into Green Bay and along the Fox and Wisconsin rivers, to the Mississippi, then down far to the Arkansas River. At this point they turned, fearing attack by Indians, paddled back and entered the Illinois River. This they followed until they came to a large Indian village near what is now the city of Ottawa, Illinois. These Indians were friendly and guided them up to the Des Plaines River where they crossed the low lying land to the Chicago River which flowed into Lake Michigan. From there they paddled north to Green Bay and returned to the starting point. The Des Plaines River flowing to the Gulf of Mexico and the Chicago River flowing into Lake Michigan were only a few miles apart, separated by Mud Lake which at some season formed almost a continuous waterway and an easy portage. The route over this portage was to be utilized by traders for the next quarter of a century.

Marquette promised the Indians to return the following year and did so spending the winter in a log cabin on the bank of the Chicago River.

In 1677 Robert Rene Cavalier, *leur de la Salle* later known as La Salle persuaded Frontenac the Governor of New France at that time to grant permission to explore the Mississippi Valley further.

He and his party came across from New France (Canada) by way of the Niagara Peninsula, northern Ohio, and Lake Michigan to the Chicago River. They crossed the portage to the Des Plaines River and proceeded down the Mississippi.



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the chief who had been given a silver medallion by Washington after the Revolutionary War formally returned the gift, indicating the displeasure of the Indian tribes. The reasons for their hostility to the Americans was not clear.

Orders came to evacuate Ft. Dearborn and remove the inmates to Fort Wayne.

William Wells was a white man who had been captured and raised from childhood by Little Turtle, Chief of the Miami Indians, and married into his family. He was greatly respected by the Indians and was selected to bring a band of thirty Miami to Ft. Dearborn to guide the inmates to Ft. Wayne. Wells advised against attempted withdrawal from the fort, fearing attack by the hostile Potawatomi under Black Partridge and other tribes. However, he was persuaded by Captain Heald then in charge to set out with the inmates on the trek to Ft. Wayne. They started out along the Lake Shore but were attacked within a few miles of the fort and all were either killed or captured. Wells was one of the first to be killed. On recognizing whom they had killed according to legend, two Indian leaders removed his heart, divided and ate it, hoping thereby to acquire some of his bravery. The step-daughter of Kinzie, the respected friend of the Indians, was saved from death at the hands of an Indian warrior. A statue showing Black Partridge saving the life of Kinzie's step-daughter from the Indians has been preserved and is now located in Lincoln Park in Chicago. The original fort was burned and nothing further is known of the region until the second fort was built four years later. Although the war of 1812-16 was over and the fort rebuilt, settlers did not come into the northern Illinois area because of hostile Indian tribes, until after the Black Hawk War.

### *The Black Hawk Wars*

Black Hawk was a chief of the Fox and Sauk tribes, whose sacred burial ground was at Rock Island, Illinois, on the Mississippi River. They had already withdrawn across the Mississippi River to Iowa but Black Hawk objected to the ceding of northern Illinois to the whites by other chiefs—some four years earlier without agreement by the Fox and Sauk tribes. He led his warriors back to Illinois and the Black Hawk War ensued in 1832. The war lasted only three months, ending with the Battle of Bad Axe near the Wisconsin-Illinois border.

By the Treaty of the Grand Council in Chicago in 1833 Black Hawk agreed to remain west of the Mississippi, and northern Illinois was open to white settlers.

A statue of an Indian by Lorado T. St., the sculptor now overlooks the Rock River at Oregon, Illinois, erroneously said to have been a statue of Black Hawk. Southern Illinois was already well settled. Illinois had become a state in 1818 and new settlers poured into the northern part.

### *The Illinois-Michigan Canal*

Meanwhile Chicago was growing and was incorporated as a town in 1833 with a population of 250 and received its first charter as a city in 1837.

The need for a canal connecting Lake Michigan with the waterway to the Gulf of Mexico had been recognized by the early explorers and was emphasized by the war of 1812 as a means of moving war equipment.

The Illinois-Michigan Canal was eventually started in 1837 and was completed in 1848. The Chicago River was thereby straightened to its present course at the

La Salle's associate Tonty an Italian known as the man with "the iron hand" one hand having been replaced by an iron hook remained in the Mississippi Valley building forts at Creve Coeur Kaskaskia and Starved Rock (Fort St. Louis) while La Salle returned to seek permission to proceed further. In 1678 he reached the Gulf of Mexico and claimed the territory for Louis XIV thereby establishing the Louisiana Territory.

After 1,000 hostile Indians blocked the portage at the Chicago River and nothing is known of the region until after 1780 when Jean Baptiste Point du Sable established a trading post on the north bank of the Chicago River near the lake.

At the mid point of the 18th century the map of North America shows the British in possession of the eastern coastal area from the Carolinas to Maine but limited by the Alleghany Mountains. The French held Cape Breton Canada northern Ohio and the broad Mississippi Valley down to the Gulf of Mexico. The Spanish held Florida Mexico and part of the southwest leaving the large area west of the Mississippi Valley unexplored. In 1759 the British took Quebec and the Treaty of Paris in 1763 ceded Canada to the British. The Louisiana Territory including the Mississippi Valley remained a French possession.

The Revolutionary War did not extend to the Mississippi Valley because of the intervening mountains. However Clark obtained permission from Patrick Henry Governor of Virginia to travel west but was afforded no help. Clark proceeded westward and captured Fort Kaskaskia but for the next four years there were Indian wars preventing further advance westward. These wars ended at the Battle of Fallen Timbers, won by Anthony Wayne known as "mad Anthony". This was followed by the Treaty of Greenville at Fort Greenville in eastern Ohio with Little Turtle Chief of the Miami Tribe.

This treaty besides opening most of Ohio to white settlement ceded a six mile-square area the present center of the City of Chicago to the U.S. The tract was never formally surveyed but it was a momentous real estate transaction in the history of Chicago.

Meanwhile Jean Baptiste Point du Sable had proven to have unusual talents. He had already established an elaborate trading post on the north bank of the Chicago River in the early seventeen eighties—with barns, a powered horse mill, many cattle hogs, poultry and sundry equipment according to the inventory as well as a collection of paintings.

### *Fort Dearborn*

The first Fort Dearborn ordered by the War Department in 1803 was built on the south bank of the Chicago River. Lt. James Strode Swearinger brought the first infantry overland from Detroit and Captain John Whistler grandfather of Whistler the artist, was put in charge.

The same year Napoleon sold the Louisiana Territory for 15 1/2 million and other considerations which concerned settlements with the Spanish.

John Kinzie a silversmith and by avocation a fur trader came to Ft. Dearborn in 1804. He spoke 7 Indian dialects. He bought the house built by du Sable and became popular with the Indians in the region.

In 1812 war broke out with England. Canada had then been under British control since the Peace of Paris in 1763. The Indians in the region of the mid west favored the side of the British and became hostile. Black Partridge one of

the chief who had been given a silver medallion by Washington after the Revolutionary War formally returned the gift, indicating the displeasure of the Indian tribes. The reasons for their hostility to the Americans was not clear.

Orders came to evacuate Ft. Dearborn and remove the inmates to Fort Wayne.

William Wells was a white man who had been captured and raised from childhood by Little Turtle Chief of the Miami Indians, and married into his family. He was greatly respected by the Indians and was selected to bring a band of thirty Miami's to Ft. Dearborn to guide the inmates to Ft. Wayne. Wells advised against attempted withdrawal from the fort, fearing attack by the hostile Potawatamies under Black Partridge and other tribes. However he was persuaded by Captain Hald, then in charge to set out with the inmates on the trek to Ft. Wayne. They started out along the Lake Shore but were attacked within a few miles of the fort and all were either killed or captured. Wells was one of the first to be killed. On recognizing whom they had killed according to legend two Indian leaders removed his heart, divided and ate it, hoping thereby to acquire some of his bravery. The step-daughter of Kinzie the respected friend of the Indians, was saved from death at the hands of an Indian warrior. A statue showing Black Partridge saving the life of Kinzie's step-daughter from the Indians has been preserved and is now located in Lincoln Park in Chicago. The original fort was burned and nothing further is known of the region until the second fort was built four years later. Although the war of 1812-16 was over and the fort rebuilt, settlers did not come into the northern Illinois area because of hostile Indian tribes, until after the Black Hawk Wars.

### *The Black Hawk Wars*

Black Hawk was chief of the Fox and Sauk tribes, whose sacred burial ground was at Rock Island Illinois, in the Mississippi River. They had already withdrawn across the Mississippi River to Iowa, but Black Hawk objected to the ceding of northern Illinois to the whites by the latter chief—some four years earlier without agreement by the Fox and Sauk tribes. He led his warriors back to Illinois and the Black Hawk War ensued in 1832. The war lasted only three months, ending with the Battle of Bad Axe near the Wisconsin-Illinois border.

By the Treaty of the Grand Council in Chicago in 1833 Black Hawk agreed to remain west of the Mississippi and northern Illinois was open to white settlers.

A statue of a Indian, by Lored Taft, the sculptor now overlooks the Rock River at Oregon Mills, erroneously said to have been a statue of Black Hawk. Southern Illinois was already well settled. Illinois had become a state in 1818 and now settlers poured into the northern part.

### *The Illinois-Michigan Canal*

Messabi Chicago was growing and was incorporated as a town in 1833 with a population of 250 and received its first harbor as a city in 1837.

The need for a canal connecting Lake Michigan with the waterway to the Gulf of Mexico had been recognized by the early explorers and was emphasized by the war of 1812-16 as a means of moving war equipment.

The Illinois-Michigan Canal was eventually started in 1837 and was completed in 1848. The Chicago River was thereby straightened to its present course at the



(See page 101)

FIG. 1. Chicago in 1833. The junction of the north and south branches of the Chicago River.

entrance from Lake Michigan. The canal was later deepened and the locks permitted the flow of water to be reversed. Navigation was established from the Lake to the Gulf of Mexico—and the avoidance of pollution of the lake from Chicago's sewage was made possible. The canal was an important factor in the early development of Chicago. It brought produce from the valley of the Illinois River to Chicago and distributed merchandise from the East to the river towns and the interior. The population rose from 20,000 in 1848 to 75,000 within six years and commerce expanded in proportion.

Although the canal made navigation possible its effect was soon overshadowed by the development of railroads. The first few miles of track of the Galena and Chicago Union Railroad eventually to become the Chicago and Northwestern system opened in the same year. The first locomotive to reach Chicago, the Pioneer, built by the Baldwin Locomotive Works in Philadelphia, is still in the possession of the Chicago and Northwestern railway. Chicago rapidly became a transportation center and within 12 years there were already eleven trunk lines coming into the city.

### *Raising of the Grades*

One of the important early developments in Chicago was the "raising of the grades." Chicago had been built on low land and in wet weather the streets were

of mud and basements flooded. The story is told that on Lake Street one day a man's head was noticed protruding from the mud in the middle of the street. On being politely asked if he needed some help he responded "No thank you, I am riding on my horse."

From 1833-1860 under the influence of George Pullman, an engineer later to develop the great Pullman Car Company, Chicago was raised out of the swamp. Sidewalks and streets had to be raised as much as four to eight feet and a drainage system developed. One large hotel was raised eight feet by the use of 2,000 jackcrews, reputedly "without spilling even a cup of tea."

A significant event of the period is Chicago was the second national convention of the Republican Party in 1860 when it nominated its first president thereby setting great American Abraham Lincoln, on the way to immortality.

Other developments were the completion of the city's first waterworks in 1865 of which the water tower still stands on North Michigan Avenue; the opening of the Chicago stock exchange in the same year and the entry of the Illinois Central Railroad into Chicago along the lake front. The first Rush Medical College building was in 1870.

### *The Chicago Fire of 1871*

The Great Chicago Fire took place in early October of 1871. Almost no rain had fallen for over three months and the winds were dry. The fire started in the O'Leary Barn but its origin has been attributed to the cow kicking over the lantern. The fire raged out of control.

The central part of Chicago including the business district was a complete ruin. 300 people died and of Chicago's 333,000 inhabitants 90,000 were left homeless.

Plans for rebuilding were begun at once. Temporary structures were built and within a few years permanent rebuilding had progressed so that few traces of the catastrophe could be found.

Rush Medical College continued in a temporary building for four years and was rebuilt in 1875, the building being replaced in 1924 by the Rawson Building.

### *The First Skyscraper*

The Chicago architect W. L. B. Jenney goes the credit for designing the first skyscraper. In earlier buildings the walls had carried the weight of the structure. As the buildings rose, height of piers to the ground had to be made thick. Ten stories called for walls four feet thick at the base and this was the practical limit.

Jenney designed a iron skeleton of columns, girders and beams to support the roof floors and walls. Valuable space formerly given over to heavy masonry was thereby saved and the walls could even be made of glass if desired. This new method was used in the Home Insurance Building, built in 1884 and revolutionized the construction industry. A brilliant era in structural engineering and the modern skyscraper were to follow.



See also p. 101

Fig. 1 Chicago in 1833. The junction of the north and south branches of the Chicago River.

entrance from Lake Michigan. The canal was later deepened and the locks permitted the flow of water to be reversed. Navigation was established from the Lake to the Gulf of Mexico—and the avoidance of pollution of the lake from Chicago's sewage was made possible. The canal was an important factor in the early development of Chicago. It brought produce from the valley of the Illinois River to Chicago and distributed merchandise from the East to the river towns and the interior. The population rose from 4,000 in 1848 to 73,000 within six years and commerce expanded in proportion.

Although the canal made navigation possible its effect was soon overshadowed by the development of railroads. The first few miles of track of the Calumet and Chicago Union Railroad eventually to become the Chicago and Northwestern system opened in the same year. The first locomotive to reach Chicago, the *Pioneer*, built by the Baldwin Locomotive Works in Philadelphia, is still in the possession of the Chicago and Northwestern railway. Chicago rapidly became a transportation center and within 12 years there were already eleven trunk lines coming into the city.

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## THE CRYSTALLOGRAPHIC STRUCTURE AND MINERALIZATION OF OTOSCLEROTIC BONE

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An analysis is presented of more than 200 bone samples. In addition  
different crystalline forms are compared with the results obtained by the  
autoradiographic method.

In our preceding study concerning the crystalline structure of otosclerotic  
bone, three types of structures were defined:

1. One which corresponds to the structure of normal human bone.
2. One with no distinctly observable crystalline structure.
3. One clearly diverging from the structure of normal human bone.

A detailed analysis of these results was carried out; the distribution of  
the material is demonstrated in Table 1.

TABLE 1. Crystalline structure of 210 samples.

Structure	Samples
Normal bone	164
Amorphous	31
Abnormal	15

All samples were removed at operations. Among the clinical findings a  
considerable variation was noticed. In most cases, the samples consisted  
of the thickened anterior part of the stapedial footplate. The samples in-  
cluded even cases in which a broad marginal thickening was noticed as well  
as cases in which the whole footplate consisted of a thick white bone with  
a rough surface. The comparison between the crystalline structure and the  
clinical findings gives no clear idea of the significance of the macroscopic  
appearance of the crystalline structure. Different shapes of the stapedial  
footplate appeared in all groups of the crystalline structure, but it seems that  
in the groups of abnormal crystalline structure there appeared more totally  
thickened footplates than in the normal crystalline structure group. This  
fact, however, has not yet been statistically proved.

All the samples in most cases were of a rather small size; they could not

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### *The World's Columbian Exposition of 1893*

A notable event in the history of Chicago's development centered around the World's Columbian Exposition planned in 1892 to commemorate the 400th Anniversary of the discovery of America. Daniel H. Burnham, Chicago architect, was in charge of the planning, enlisting the help of the most famous architects, sculptors and landscape designers of the country. The plan transformed Jackson Park and the Midway, later to become the site of The University of Chicago, from a swamp to a fairyland.

The exposition attracted 27 1/2 million people in the six months that it was open—almost half the number of people living in the United States. It displayed the beauties of classic architecture, starting a trend that was to last for a generation.

A unique attraction was the giant "Ferris" wheel built by Ferris to provide a view of the panorama from a maximum height of 250 feet.

The Art Palace was preserved, completely rebuilt in stone and is now the Museum of Science and Industry. The Midway has become the home of The University of Chicago.

### *The Chicago Plan*

The plan developed by Burnham and his associates for the Columbian Exposition was expanded in succeeding years and was published by the Commercial Club of Chicago in 1909 as "The Chicago Plan." This comprehensive plan took in all of Chicago and the surrounding country for a radius of about 60 miles. The preservation of the lake front including Jackson Park, Grant Park, the Museums, Lincoln Park, the forest preserves and many smaller parks were all a part of this plan.

Chicago has grown rapidly and now has a population of over 6,500,000 people in the metropolitan area. It seems almost incredible that only 130 years ago it received its charter as a city with only a few thousand inhabitants. It is only 140 years since some of the countryside that you will drive through this week was still the land of the Potawatomies, the Fox, the Sauks and other Indian tribes.

### ACKNOWLEDGMENT

The author is indebted to the Chicago Historical Society for illustration and much information concerning the early history of the Chicago region.



FIG. 2. Micrograph of an osteosclerotic footplate with morphic crystallographic structure. Low mineralization. Diffuse texture.



FIG. 3. Micrograph of an osteosclerotic footplate with normal crystallographic structure. High mineralization. Some osteocytes.



Fig 1 Microradiogram of an articular footplate with normal crystallographic structure. High mineralization.

be histologically examined. However, the same samples could be used for a microradiographic examination. This work is still continuing.

Up to the present time, 40 samples have been microradiographically examined. Of these, the crystallographic examination showed normal crystalline structure in 34 cases, in 3 cases the structure was amorphous and in 3 cases it was pathological. The soft-ray microradiography technique was used. The bone pieces were embedded into methylacrylate and then cut into slices of 50–100  $\mu$ . For the microradiographical examination 20 kV were used, the film being Kodak Maximum Resolution Plates.

In spite of the limited extension of the material, it is already possible to make some observations at the present stage. In the samples with normal crystalline structure, a clear mineral content could be observed. The grade of this, as well as of the osteocytes, varied very much. In the amorphous group, the mineral content was obviously less than in the other groups. For this reason, no microradiographic patterns could be obtained of part of the samples.

In the group showing a pathologic crystalline structure, the mineral content varied highly, as well as in the normal groups.

In the following, some microradiographic pictures will be presented (Figs 1, 2 and 3).

The results at the present moment are showing a correspondence between the crystallographic findings and the microradiographic pictures.

## ARE THERE COCHLEAR SHUNTS IN PAGET'S AND RECKLINGHAUSEN'S DISEASE?

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In 14 petrous bones from 14 cases of Paget's osteitis deformans and Recklinghausen's osteitis fibrosa, foci of diseased bone replace the endosteal layer of the bony otic capsule. The petrous bones demonstrate changes in the stria vascularis in the form of circumscribed swelling and flat thickenings, as described by M. Kornfeld. In contrast to the striae in otosclerosis, the striae changes in osteitis deformans and osteitis fibrosa also occur in areas where the normal endosteal layer still remains intact. There is no evidence of shunts in the spiral ligament of any of these temporal bones to cause the changes in the stria. Also, no new lamellar bone deposits could be seen at the attachment of the spiral ligament. On the other hand, in 8 petrous bones with Paget's and Recklinghausen's disease there are several slender shunts in the basal turn of the cochlea, connecting the capillaries of the diseased bone with the spiral veins. In these cases, however, only one case are there signs of venous congestion in the inner ear. In 13 petrous bones with osteitis deformans and osteitis fibrosa large shunts are seen in the internal auditory meatus between the vessels of the diseased bone lining the meatus and the internal auditory vessel within the canal. A marked thickening of the endosteal connective tissue provides evidence of venous congestion in the internal auditory meatus, due to the shunts. These shunts, causing a circulatory disturbance in the internal auditory meatus, may be responsible for the sensorineural deafness in Paget's and Recklinghausen's disease.

The striking similarity of the histological picture in otosclerosis and in Paget's osteitis deformans was first observed by Otto Meyer in 1913. Since then various authors have confirmed that otosclerosis, Paget's disease and Recklinghausen's osteitis fibrosa have many histological features in common. Vager & Meyer (1932) have concluded that the rigid and rather poorly reactive bony tissue may respond in the same way to a number of different disease processes. First, a new osteoplastic bone marrow is laid down. The old bone then undergoes osteoclastic destruction to be replaced by a network of unripe bone poorly supplied with fibrils, which is later remodelled into lamellar bone. In Paget's disease the bone shows a tremendous increase in the number and diameter of the small blood vessels.

The samples with a lack of or an obscure crystalline structure either had an obviously lower mineral content than those of the other groups, or even none.

In this way these microradiographic measurements are confirming our previous presumption that the amorphous samples refer to otosclerotic foci, from which the normal bone structure has disappeared and the new ossification is starting. The problem of the pathologic crystalline structure is, nevertheless, still unsolved.

### RÉSUMÉ

Une analyse est présentée de plus de 200 échantillons osseux. De plus, les différentes formes de cristaux constatées sont comparées avec les résultats obtenus par la méthode microradiographique.

### ZUSAMMENFASSUNG

Eine Analyse von mehr als 200 Knochenproben wird dargelegt. Ausserdem werden verschiedenartige Formen der Kristallstruktur mit den durch mikroradiologische Methoden gezeigten Ergebnissen verglichen.

### REFERENCES

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### DISCUSSION

G. E. Shambagh: The etiology of the common and mysterious condition known as otosclerosis continues to elude us. Mr. Meurman states that his studies have not solved the mystery. However, we must keep in mind that we are dealing not with a sclerosis but rather an osteoporosis. The lesion occurs in the dense endochondral bone of the labyrinthine capsule. Everywhere else in the skeleton bone undergoes constant remodelling. Only in the endochondral bone of the labyrinthine capsule does the adult possess bone completely inert and free from remodelling, actively once it was laid down in foetal life. It is in this inert bone that the otosclerotic lesion arises as a focus of new bone with very active remodelling. It is to convert this actively enlarging focus to dense bone more like that of the normal endochondral capsule that Mr. Petrovic and I have been conducting the studies that he will report on Thursday. Let us remember when ever we speak of "otosclerosis" that we are actually talking about the exact opposite—a localized osteoporosis of the labyrinthine capsule.

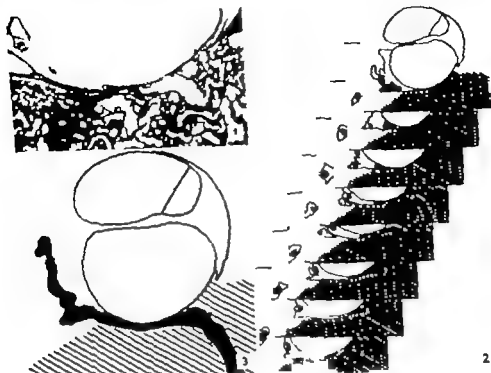


Fig. 1. Male patient L, 23 years old. Vertical section through the basal turn of the left temporal bone showing large deposit of otosclerotic bone bordering the scala tympani. Shunt between otosclerotic mass and inferior spiral line.

Fig. 2. Same case. Fig. 1. Reconstruction of the course of the ossal level plane.

Fig. 2. Same case as Fig. 1. Reconstructed shunt between the focus of otosclerosis and the grossly dilated placenta.

Hornfeld made a histological study of 7 temporal bones with Paget's osteitis deformans with the following results:

In 2 temporal bones the process was mainly restricted to the periosteal layer. The endosteal layer was intact. The stria vascularis was found to be normal in these temporal bones. In a second group of 5 temporal bones all layers of the labyrinthine capsule were severely affected and the abnormal bone had reached the cochlear endosteum at many points. In all bones of this group the stria showed abnormalities. Most commonly a circumscribed swelling either in the form of a flat thickening or of a pedunculated nodule were found, both consisting of small blood vessels and stria epithelium. Hornfeld tried *without* success to find shunts between the blood vessels of the Paget bone and the blood vessels of the inner ear similar to the shunts we have found in otosclerosis.

In connection with Hornfeld's work we have examined our own specimens of Paget's disease (12 cases, 17 petrous bones) and Recklinghausen's osteitis fibrosa (2 cases, 4 petrous bones).

The exuberant vascularity of an actively growing focus of otosclerosis has been repeatedly described by otolhistologists. Every deposit of otosclerosis develops its own more or less independent vascular system which arises in several places from the arterial capillaries of the normal otic capsule and drains back again into the venous capillaries. Anson & Bast (1949) have shown that there is normally *no* vascular connection between the vessels of the bony otic capsule and the blood supply of the membranous labyrinth.

In 1964 we observed changes in the stria vascularis in relation to foci of otosclerosis growing through the endosteum of the otic capsule and bordering directly against the spiral ligament. These changes in the stria consisted of a circumscribed increase of vascular loops and a proliferation of the stria epithelium. So-called shunts, or pathological vascular connections, were seen between the vascular spaces of the otosclerotic focus adjoining the ligament and the spiral capillaries running through the ligament itself. Further shunts were also demonstrated in the basal turn of the cochlea between otosclerotic vessels and the spiral veins of the inner ear. These shunts cause venous congestion of the inner ear pending the gradual enlargement by osteoclasts of the normally narrow bony canals transmitting the veins across the otic capsule. As long as the venous congestion persists increasing damage to the inner ear may result. It is probable that the sensorineural deafness in otosclerosis is due to the shunts causing venous congestion of the cochlea. Following a suggestion by Mr Anson several shunts were reconstructed from otosclerotic ears by my collaborator Jürg Mann. One example was demonstrated at the Workshop in 1967. Here we have a second example.

In a patient, 25 years of age the vertical section through the basal turn of the left temporal bone (Fig. 1) shows a large shunt between the vessels of an otosclerotic focus in the basal turn and the inferior spiral vein. Reconstruction of the course of these vessels on a level plane (Fig. 2) shows a wide shunt arising from the focus of otosclerosis and draining into the grossly dilated spiral vein and the equally dilated vein of the cochlear aqueduct (Fig. 3).

Following up our histological findings, Kornfeld (1967) correctly made the demand

Since there is a considerable histological similarity between otosclerosis and Paget's disease it would seem reasonable to assume that inner ear changes in Paget's disease would resemble those in otosclerosis if the underlying osteodystrophy affects the same portions of the labyrinthine capsule. If shunts between the capsular and cochlear circulation in otosclerosis are as frequent as claimed by Rüedi it is to be expected that they would be at least equally frequent in Paget's disease because in the latter there is evidence for the presence of multiple arteriovenous communications in various diseased bones of the body.

completely replaced by diseased bone in several places. Pathological changes in the stria vascularis were seen in this group only involving 9 petrous bones and consisting of circumscribed or diffuse thickenings, atrophy and cysts, as noted by Kornfeld. The structure, but not the localization, of the circumscribed thickening resemble the stria changes seen in otosclerosis. The swellings of the stria in otosclerosis are confined to the area where the otosclerotic bone comes into direct contact with the spiral ligament. In osteitis deformans or fibrosa, however similar stria changes are also seen in the region where the endosteum bordering on the spiral ligament is still intact. Histological evidence offers no explanation for the stria changes in osteitis deformans or fibrosa. Kornfeld's findings are confirmed in that there is no evidence of shunts in the region of the spiral ligament and no other signs of venous congestion. In particular no new deposits of lamellar bone could be demonstrated.

On the other hand, we have found undoubted evidence of shunts between the vessels of the inner ear and the vessels in the diseased bone in 8 petrous bones with Paget's and with Recklinghausen's disease. These shunts were situated in the basal turn of the cochlea which is also the favourite site for shunts in otosclerosis.

A 70-year-old patient with Paget's disease (Case No. 2) shows a deposit of diseased bone penetrating the endosteum of the left basal turn of the cochlea, seen here in horizontal section. There is a slender shunt (Fig. 5) between the fine vessels of the osteitis deformans and the inferior spiral vein. This shunt has been demonstrated already at the 3rd Workshop in Chicago.

A larger shunt is present in a 33-year-old case of Paget's disease (No. 1) between the vessels of the bone and the inferior spiral vein, again in the basal turn of the cochlea (Fig. 6) near the origin of the calcified aquae ductus cochleae.

Finally another convincing shunt appears, again in the basal turn of the cochlea (Fig. 7) in a 34-year-old case (No. 14). The opened marrow spaces of the modiolus, which is still surrounded by normal bone, show newly formed pinkish osteoid tissue which is being laid down as a result of congestion. The deeper layers of the same temporal bone reveal further evidence of increased circulatory activity in the markedly dilated inferior spiral vein. Apart from this last example the few slender shunts present in the basal turn of the cochlea in the remaining temporal bones have not given rise to any congestion of the spiral vessels.

Since we have discovered an arterial shunt in the internal auditory meatus from a case of otosclerosis, we have also made a careful search of this area in the cases of Paget's and Recklinghausen's disease.

In 16 petrous bones the diseased bone replaces the normally dense nodular layer of the internal auditory meatus. In spite of this filling in with pathological bone the lumen of the internal auditory meatus is only slightly reduced in one case (No. 3). In the remaining cases the bony



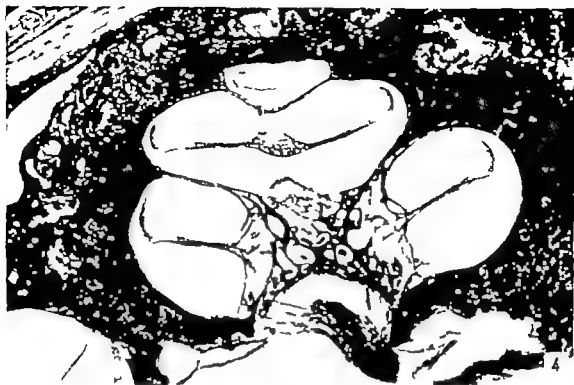


FIG. 4 54-year-old case of Paget's disease (No. 14)

After Kornfeld's excellent description of the pathological changes in the bone structure of the petrous bones any repetition would be superfluous. In spite of the many points of similarity between the histological pictures of the temporal bone in Paget's and Recklinghausen's disease they are generally quite easy to distinguish from otosclerosis. It is well known that the changes in the bone structure in otosclerosis are confined to the human bony otic capsule. To begin with foci are laid down in the enchondral layer and extend from there to involve both the endosteal and the periosteal layers. In contrast Paget's and Recklinghausen's disease both affect different bones and the entire bony skull. Having involved the base of the skull the disease may advance to attack the petrous bone on a broad front. In a 54-year-old case of Paget's disease (No. 14) the diseased bone surrounds the hard bony otic capsule (Fig. 4). The periosteal layer has first been attacked, then the enchondral layer and finally the endosteal layer has been replaced with diseased bone. As a result of the changed static condition in the region of the base of the skull and the petrous bone spontaneous fractures commonly occur in the otic capsule.

Our histological findings in the bony otic capsule and the pathological changes in the neuroepithelial elements of the inner ear are summarized in Table 1. We will only comment on the condition of the stria vascularis and the demonstration of shunts between the vessels of the inner ear and those from the bone in osteitis deformans or fibrosis.

In 14 petrous bones the endosteal layer of the bony capsule has been

Organ of Corti	Ganglion cells	Bony cochlea	Nerves nervus intermedius
Small layer of indiff. cells	Reduced in basal turn. Hemolysis	Shunt. Fractures	Surrounded with pathologic dope. Big shunts
Small layer of indiff. cells	Reduced in basal turn	Shunt. Fractures	Surrounded. Shunts
Normal	Reduced in basal turn	Shunt. Fractures	Surrounded. Big shunts
Postmortal disintegration	Normal		Surrounded and somewhat narrowed. Shunts
Postmortal disintegration	Normal		Surrounded. Shunts
Normal	Normal		Surrounded. Shunts
Postmortal disintegration	Normal		Surrounded
Postmortal disintegration	Normal	Shunt	Surrounded. Big shunts
Normal	Reduced in basal turn		Surrounded. Big shunts
Postmortal disintegration	Normal		Normal
Shunt in all turns	Reduced in all turns		Surrounded. Shunts secondary reduced
Shunt in all turns	Reduced in all turns		Surrounded. Shunts secondary reduced
Postmortal disintegration	Normal		Surrounded. Shunts
Postmortal disintegration	Reduced in all turns		Normal
Postmortal disintegration	Reduced in all turns		Normal
Normal	Normal		Normal
Normal	Normal	Shunt	Surrounded. Shunts
Normal	Normal		Normal
Normal	Normal	Shunt. Fractures	Surrounded. Big shunts
Shunt in basal turn	Reduced in basal turn		Surrounded. Big shunts
Postmortal disintegration	Reduced in basal turn		Surrounded. Shunt

TABLE 1

Name	Age	Hearing	Diagnosis	Endost	Stria vascularis
1 T B	73 y	For 3 yrs. has had slight diminution of hearing	Paget	R. Replaced by pathologic bone L. Replaced	Narrow Few hyaline blood vessels independent of path. bone Narrow Few hyaline blood vessels independent of path. bone
2 H R.	79 y	?	Paget	R. L. Replaced	Normal
3 K P	69 y	?	Paget	R. Replaced L.	Postmortal disintegration
4 St B	80 y	?	Paget	R. Intact L. Replaced	Normal Cysts. Enlarged vessels. Circumscribed atrophy independ. of pathologic bone
5 R. A	71 y	?	Paget	R. Intact L. Replaced	Normal Normal
6 M	79 y	?	Paget	R. Replaced L.	Narrow Localized atrophy
7 B A.	50 y	?	Paget	R. Intact L.	Normal
8 H L.	75 y	?	Paget	R. Replaced L. Replaced	Narrow Indifferentiated layer in all turns Narrow Indifferentiated layer in all turns
9 G	36 y	?	Paget	R. Intact L.	Postmortal disintegration
10 Ch T	56 y	?	Otitis fibrosa Recklinghausen	R. Intact L. Intact	Postmortal disintegration Postmortal disintegration
11 B U	77 y	Deaf	Otitis fibrosa Recklinghausen	R. Replaced L. Replaced	Circumscribed thickenings independent of pathologic bone Circumscribed thickenings independent of pathologic bone
12 B. H	90 y		Paget	R. Intact L.	Normal
13 H. G	78 y	Deaf Conversation possible without difficulty	Paget	R. Replaced L. Replaced	Normal Normal
14 O	54 y	?	Paget	R. Replaced L.	Cysts. Postmortal disintegration



FIG. 7. 84-year-old case of Paget's disease (No. 14). Shunt between the vessel of the Paget-bone and the vessel of the modiolus.

FIG. 8. 78-year-old case of Paget's disease (No. 13). Numerous shunts between the lumen of the Paget-bone and the internal auditory vein.

shunts between the veins in Paget's bone and the widely dilated internal auditory vein (Fig. 8). The endosteal connective tissue becomes greatly thickened as a result of this chronic venous congestion.

The fact that these large shunts between the vessels in the diseased bone and the cochlear vessels within the internal auditory meatus are very common in Paget's disease raises the question whether the blood circulation in the modiolus may be disturbed by a peripheral extension of this congestive process.

One may further question whether changes in the ganglion cells may arise and possibly also whether changes in the perilymph may occur as they do in acoustic tumours. Our histological material does not provide the answers to these questions. There are no details concerning the hearing in our cases. The histologically established changes in the neuroepithelial element of the cochlea could be accounted for by the age of our 60- to 80-year-old cases. Lindsay & Perlman (1936) have reported 4 patients with otic deformans with hearing impairment. All showed some sensorineural loss in all frequencies with a more severe loss in the high frequencies. Also Sparrow & Duxall, III (1967) described 5 further cases of Paget's disease with hearing impairment. Apart from 2 cases with conductive deafness, all cases showed a sensorineural hearing loss. In contrast with sensorineural deafness in otosclerosis the hearing loss in all these cases only began when the disease was well advanced. Again, in contrast with otosclerosis, Sparrow & Duxall's cases also showed a sensorineural loss in all frequencies. Further audiological tests, especially speech discrimination audiometry, should help to solve the question whether the sensorineural deafness in otic deformans or fibrosa could be caused by venous congestion within the internal auditory meatus resulting from shunts in this region.



FIG. 5. 79-year-old case with Paget's disease (No. 2). Slide showing the relationship between the vessels of the osteoid and the internal auditory nerve.

FIG. 6. 73-year-old case of Paget's disease (No. 1). Large shunt between the vessels of the Paget bone and the internal auditory nerve.

meatus is of normal width. Moreover, in 15 temporal bones we have found large shunts between the vessels of Paget's bone and the internal auditory vessels, running alongside the nerve within the canal. These shunts are in our view of some importance for the spatial relations within the internal meatus.

In the 78-year-old case of Paget's disease (No. 13) there are numerous

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## DISCUSSION

*C. Kelemen* After mentioning examples of shunt in Paget of the temporal bone the fact is described that the wall of the facial canal is formed frequently to a large extent by otosclerotic bone without damage to the facial function. It is difficult to imagine that the same substance shunted into the cochlea should damage the cochlear end-organ leaving the facial intact.

*J. R. Lindsay* I wish to show some slides from an elderly case of Paget's disease associated with profound bilateral deafness. These slides confirm the observation of multiple "shunts" described by Mr Rüedi. They illustrate a second fracture through the bony capsule at the region of the round window and the posterior canal ampulla. These are associated with a hyperplastic reaction in the perilymphatic spaces consisting of extensive fibrosis. The fibrosis is related to the areas where the defect in the bone involves the peribony layer.

The question which is raised and as yet unanswered by the histopathology at the present stage of our information is how to interpret the relation of the lesion to the disturbance of function. Is the disturbance in circulation the predisposing factor or is the evidence of an irritative reaction caused by the focus the more important factor?

*W. House* Injection technique in the temporal bone has shown that the internal auditory artery supplies more than just the inner ear. If this is true do you feel enough congestion of the internal carotid artery?

*C. Stannough* Mr Rüedi has, for the first time given us a logical explanation for the sensori-neural loss that occurs in the majority of cases of stapedial otosclerosis, and in pure cochlear otosclerosis. I have been impressed by the tendency of the sensori-neural loss to progress for time and then to stabilize in at least some cases. If the sensori-neural loss is due to nutritional or oxygen deprivation of the hair cells produced by a shunt does this mean that shunt can shut down or disappear after time?

*L. Rüedi (Reply)* to Mr Kelemen You put the question: what strange material circulating through the shunts in otosclerosis? First, we have to define the expression shunt. "Shunt" means histologically visible connection between arterial or venous blood vessels. Therefore within the lumen of a shunt blood is circulating.

## RESUME

Dans 14 rochers de 14 cas d'ostitis deformans Paget et d'ostitis fibrosa Recklinghausen la partie endostale de la capsule labyrinthique est remplacée par l'os pathologique. Dans ces rochers la stria vascularis présente les altérations décrites par M. Kornfeld sous forme d'ensures localisées et d'épaississements allongés. Il n'y a pas des shunts dans le ligamentum spirale qui pourraient être la cause de ces altérations. Dans 8 cas de maladie de Paget et Recklinghausen on trouve par contre dans la spire basale quelques petits shunts reliant les capillaires de l'os pathologique aux veines spirales. Seulement dans 1 cas il y a des signes de congestion veineuse. 15 rochers présentent des grands shunts au niveau du méat acoustique interne entre des vaisseaux sanguins de l'os pathologique de la paroi et des vaisseaux labyrinthiques dans le méat. Un élargissement endostal suggère l'existence d'une congestion vasculaire. Il est possible que la surdité de perception dans les cas d'ostitis deformans et d'ostitis fibrosa soit causée par des troubles circulatoire due aux shunts dans le méat acoustique interne.

## ZUSAMMENFASSUNG

In 14 Felsenbeinen von 14 Fällen mit Ostitis deformans Paget und Ostitis fibrosa Recklinghausen ersetzt der kranke Knochen stellenweise die endostale Schicht der knöchernen Schnecken Kapsel. In diesen Felsenbeinen sind die von M. Kornfeld beschriebenen Veränderungen der Stria vascularis vorhanden in Form von umschriebenen Anschwellungen und leistenförmigen Verdickungen. Im Ligamentum spirale dieser Felsenbeine können keine Shunts als Ursache der Striaveränderungen nachgewiesen werden. Hingegen finden sich in 8 Felsenbeinen mit Ostitis deformans und Ostitis fibrosa ebenfalls in der basalen Schneckenwindung einige zarte Shunts, welche die Kapillaren des kranken Knochens mit den Venen spirales verbinden. Anzeichen einer venösen Innenohrstauung sind nur in 1 Fall vorhanden. Ausserdem sind in 15 Felsenbeinen mit Ostitis deformans und Ostitis fibrosa im Meatus acusticus internus grosse Shunts zwischen den Gefässen des kranken den Meatus begrenzenden Knochens und den im Meatus verlaufenden Innenohrgefässen vorhanden. Für eine shunt bedingte Abflussstauung im Meatus acusticus internus spricht eine Verbreiterung des bindegewebigen Endostes. Möglicherweise entsteht die Perzeptionsschwerhörigkeit der Ostitis deformans und der Ostitis fibrosa infolge einer shunt bedingten Zirkulationsstörung im Meatus acusticus internus.

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## DOMINANT HEREDITARY CONDUCTIVE DEAFNESS THROUGH LACK OF INCUS-STAPES JUNCTION

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This report concerns an extensive family research in which a regular dominant conductive deafness can be traced in four generations. The middle-ear operation of four ears on three symptom-carriers showed a missing connection of the incudo-stapedial joint.

Reference is made to the fundamental research work of Anson Bost and collaborators, regarding the differentiated evolution of the middle ear ossicles and the incudo-stapedial function. In this small malformation of the middle-ear ossicles it must be assumed that in affected members dominant genetic factor prevents in the sixth to the seventh fetal week the rotation and the joint of the distal end of the incus with the blastema of the stapes, the result is an inborn conductive deafness.

In cases of conductive deafness with a normal ear-drum, normal pneumatization and no symptoms of inflammation, we diagnose generally an otosclerosis. During the operation we sometimes discover another cause such as congenital fixation of the stapes or aseptic necrosis of the incus-stapes junction. At the Detroit Symposium of Otosclerosis I mentioned a family tree with otosclerosis over three generations and congenital stapes fixation in the fourth generation, with the interpretation that the same hereditary factor may lead to otosclerosis or congenital stapes fixation.

Today I deal with another familiar ear deformity. It is to the credit of Ombredanne (1940, 1960, 1962, 1964) that he elaborated the conception of small malformations in the middle ear. One of the predominant areas of malformation is the incus-stapes joint, as is confirmed by Hough (1948, 1952, 1963), Kelly (1968), Tolan & Wilson (1948), Henner (1960) and Sooy (1960). Morphological variations at this place are not so seldom. But already before 1916 Anson & Bost (1916) mentioned that one should be extremely critical in the interpretation of these variations a pathological facts. Because of the maturation of the ossicles attained during the fetal period, and the profound change of the origin elements prior to the definite construction of the ossicle-chain, variations may occur occasionally. Only the missing junction of the incus-stapes joint is pathological.

It is an honour for me to express my admiration for and homage to the scientific work of Anson & Bost (1916) and co-workers. All our know-



to Mr *Lindsay* After demonstrating a case of Paget's disease you asked if the productive labyrinthitis is produced by some chemical agent or due to a large fracture or as in otosclerosis due to venous stasis? In our cases of otosclerosis with productive labyrinthitis lamellar bone formation probably caused by venous congestion was always present As far as I could see there is no lamellar bone formation present in the Paget's case and there are no other signs of venous congestion The cause of the productive labyrinthitis is unknown to me

to Mr *W House* The endosteal layer of the bony otic capsule is histologically a closed barrier Biochemically this barrier may be insufficient But only after the formation of shunts can a great quantity of venous blood flow into the soft tissues of the inner ear producing here a stasis until the channels in the bony otic capsule are dilated

to Mr *Shambaugh* A shunt once developed may close again when the otosclerotic focus becomes inactive and lamellar is filling up the narrow spaces. Other shunts may stay open but the damage to the inner ear stops as soon as the bony channels leading the blood vessels from the membranous labyrinth to the venous sinuses are sufficiently enlarged to overcome the blood stasis within the inner ear spaces.

## **DOMINANT HEREDITARY CONDUCTIVE DEAFNESS THROUGH LACK OF INCUS-STAPES JUNCTION**

**F. ESCHER, M.D. and H. HIRT, M.D.**

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FIG 1

FIG 1 Primitive joint between Reichert cartilage to the blastema of the incus body Fifth fetal week (Anson & Bass, Strickland and co-workers)

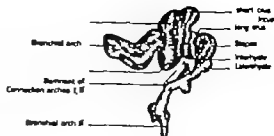


FIG 2

FIG 2 Secondary reunion between the long crus of the incus to the stapes Sixth to the seventh fetal week.

ledge and the modern embryologic conception of the visceral descent of the middle ear is based on the imposing investigations of these authors. Thus the malleus and incus are not totally descending from the first visceral arch, but only the head and the neck of the malleus and the body of the incus. The manubrium of the malleus and the long crus of the incus belong to the second arch. There is a first primitive joint—a bridge—between Reichert's cartilage to the blastema of the incus body in the fifth fetal week. This joint dissolves and, during the sixth to the seventh fetal week, a secondary reunion arises between the long crus of the incus to the stapes. This astonishing development and the attraction of the two bony surfaces of the small ossicles, end in a back differentiation in a mesenchymal tissue, from which, in the 23rd week only the cartilage and definitive incus-stapes joint is created. This highly differentiated mechanism progresses with incredible precision. Variations are not so seldom, but the missing joint is a rarity. Genetic factors are mentioned, but genealogic investigations are unknown. Hanhart (1949) describes family trees with higher deformities, such as atresia auris associated with palatoschisis.

#### *Description of a family with juvenile conductive deafness caused by lack of joint between incus and stapes*

The first observation concerns a man born in 1932 (1204/62) with bilateral conductive deafness, normal ear-drums and normal pneumatization. Under the diagnosis otosclerosis or congenital stapes-fixation, we performed a middle ear revision on the left side but to our surprise we observed the following deformity:

The long crus of the incus was curved like a hook; the head of the stapes was lacking and there was no connection between the incus and



FIG. 2. Status of the three operated ears with missing connection between incus and stapes.

FIG. 3. Photograph of the incus with hook on the distal end.

the mobile stapes. A new junction from the stapes to the malleus gave a good functional result.

Some months later the right ear was operated on and its status was exactly the same.

The shortened long crus of the incus was like a hook. Some small fibres of connective tissue to the reduced head of the stapes were present. The restored ossicle-chain gave an excellent functional result. The patient informed us that his two brothers have had a similar hearing loss since youth. We had an opportunity to perform a middle ear revision in the ear of one of his brothers.

A. S. 525 B3. Here too, the status was of the same kind: stapes with small head, and curved distal end of the long crus of the incus with a fine band of connective fibres.

The histology of two incus shows that no signs of inflammation exist. There is a normal structure of bony tissue with marrow canals and a normal vascularization. From a marked and fine limited zone in the distal end—like a nest—connective fibres take their origin.

On the basis of these hard-of-hearing brothers, we started genealogic investigation and we established a complete family tree over five generations beginning in the early 19th century with 342 members. Except for four members, we had information on hearing function in all cases. It is extremely interesting that bilateral juvenile conductive deafness starts with one member (10) in the second generation. Only direct descendants from this female proband are affected. A healthy-born member never has a case of this type of deafness in the next generation.

In 12 cases juvenile deafness was found. The living hard-of-hearing members of the generations III, IV and V had a complete audiometric investigation.

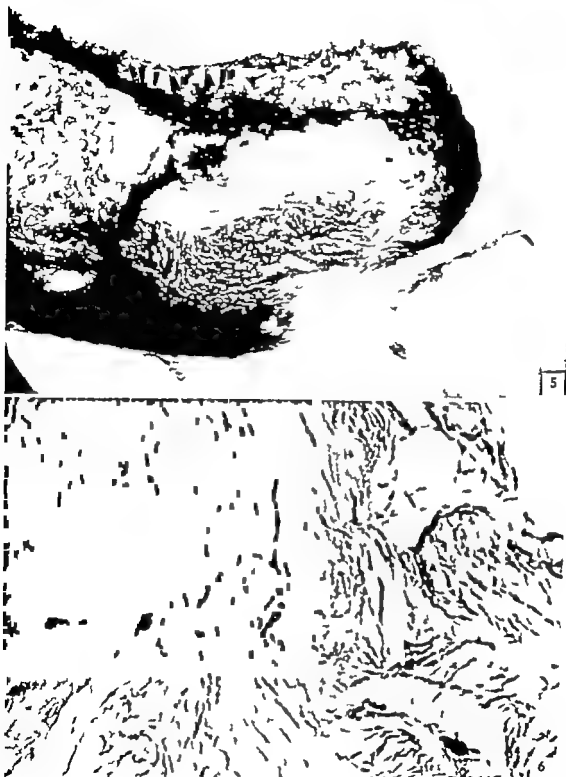


FIG. 5 Collagen fibres, H&E stain, distal part of the linea

FIG. 6 Fine lamellated bands between connective tissue and ligamentous inflammation

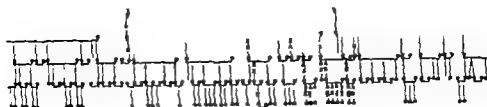


FIG. 7 In part of the family tree ■● Juvenile conductive deafness.

Furthermore, it may be of interest that all affected members, with one exception, have hypertrophic and thickened ear lobules. It is probable that this associated symptom is attached to the same dominant genetic factor in the sense of polyphony.

Further ear revisions are planned, the next on a child of the fifth generation. This operation was performed in Nov 1938. The same status of lacking incus-stapes junction was found. We hope to confirm in these cases our following conclusions:

1. In each case of bilateral juvenile conductive deafness one of the parents is a holder of the same syndrome. A generation is never left out. All holders of the gene are simultaneous holders of the syndrome. There is complete penetrance and a regular dominance.

2. The frequency of the gene holders in the descendence amounts to 50%.

3. The descendence of healthy members is, in each case, free from the syndrome. The hereditary path in generations I and II cannot be judged. In particular we do not know if the first member II/10 has already a hereditary deafness, or if it happened in this case to be a dominant mutation.



FIG. 8 Associated symptom of affected members hypertrophic and thickened lobules.

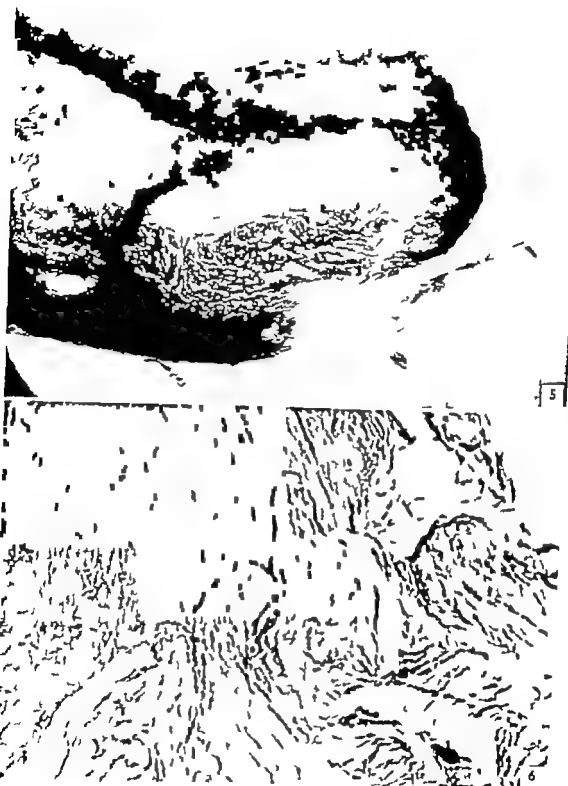


FIG. 5. Connective fibres like a nest, in the distal end of the incus.

FIG. 6. Fibrous borderline between connective tissue and longitudinal inflammatory

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4 The syndrome is independent of sex.

5 We have to assume that in affected members a dominant genetic factor prevents in the sixth to the seventh fetal week the rotation and junction of the distal end of the incus with the blastema of the stapes, resulting in inborn conductive deafness.

### RESUME

Rapport sur une investigation généalogique d'une famille dans laquelle existe au cours de 4 générations une surdité de transmission congénitale bilatérale de dominance régulière. La révision de 4 oreilles de trois porteurs du syndrome montre une jonction déficiente entre l'enclume et l'étrier. Les travaux embryologiques du développement de l'oreille moyenne de Anson, Bast et collaborateurs permettent de comprendre le mécanisme différencié de la formation de l'articulation incudostapédienne. Pour nos probands il faut admettre un facteur génétique qui a empêché la rotation de la branche longue de l'enclume et l'union avec l'étrier entre la 6<sup>e</sup> et la 7<sup>e</sup> semaine fœtale d'où résulte la surdité de transmission congénitale.

### ZUSAMMENFASSUNG

Es wird über eine ausgedehnte Familienuntersuchung berichtet, in der eine regelmäßig dominante Schalleitungsschwerhörigkeit in 4 Generationen nachgewiesen werden kann. Die Mittelohrvision bei 3 Merkmalsträgern an insgesamt 4 Ohren ergab einen fehlenden Schluss am Amboss-Steigbügelgelenk. Es wird auf die grundlegenden Untersuchungen von Anson und Bast und ihren Mitarbeitern hingewiesen, welche die differenzierte Entwicklung der Gehörknöchelchen und der Amboss-Steigbügelverbindung eingehend darlegen. Es muss bei dieser Störung angenommen werden, dass ein erblicher Faktor bei den Probanden eine Drehbewegung und Vereinigung des Ambosschenkel mit dem Steigbügelblastom in der 6-7 Foetalwoche gestört hat, so dass die congenitale Schalleitungsstörung entstand.

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## MOVEMENTS OF THE VOCAL CORDS

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Vocal cord movement induced by laryngeal nerve stimulation was compared with that of respiration, phonation and deglutition and the results of electrical stimulation of the external superior laryngeal and recurrent nerves and their branches in dogs at different frequencies and voltages are described. The posterior cricoarytenoid muscle (abductor) has a low frequency characteristic when compared with the adductor muscles. The frequency characteristics of the cricothyroid muscle (tensor) is between the abductor and the adductor.

Abduction and adduction of the vocal cord in the phases of respiration, phonation and deglutition appear to be simple. Actually its neurophysiologic responses are not readily explained nor clearly understood. Anatomical and physiological correlation by means of electrical stimulation of the human superior laryngeal nerve was observed by Ogura & Lam in 1953.

Nakamura *et al.* (1950, 1961, 1963) observed that the use of low frequency stimulating currents on the recurrent laryngeal nerves caused the opening of the glottis while higher frequency currents closed the glottis, and this phenomenon was also observed by Brewer & Dana (1963) and Hall (1966) although no satisfactory explanation was given. These experiments were performed to explore the mechanism of this phenomenon as well as add further information in regeneration of the recurrent laryngeal nerves in our larynx transplantation studies (Ogura *et al.* 1966, 1967).

### EXPERIMENTAL METHODS

The experiments were carried out on 6 dogs. In the supine position, anterior pharyngeal exposure of the larynx was obtained using intratracheal anesthesia with Sodium Pentobarbital. After removal of the ligand bone the sternohyoid and sternothyroid muscles were divided from their superior attachment and then the anterior wall of the hypopharynx was opened to obtain a direct view of the glottis.

Electromyographic recording of the laryngeal muscles was made by

This study was supported by NIH Grant N.B. 04200

## DISCUSSION

*P Livingstone* The gap between stapes and deformed incus is not always due to a genetic cause. The condition is more common in those cases where the cause is teratogenic and occurs in about 16% of cases. How does fat get into the middle ear in these cases of *mental atresia*?

*F Sooy* I have noticed that you have used polyethylene tubing in reconstructing these cases and would like to ask if you have found this to be a lasting technique and if not do you now use another method in the management of such cases?

*F Escher (Reply)* to Mr *Livingstone* The variety of middle ear malformations is very high. The special and unknown situation in our family is the fact that the small malformation of lacking an incus-stapes joint is identical in different members and that this phenomenon has a dominant heredity.

to Mr *Sooy* Plastic material for repair of the ossicle chain was used three years ago. Now we prefer to employ the turned original incus for a columella effect.

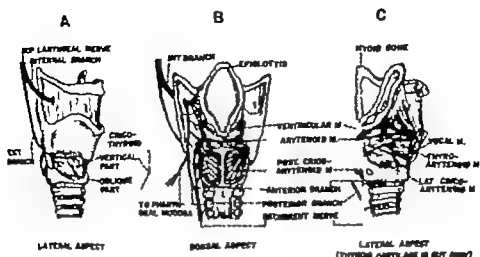


FIG. 1. These figures show musculature and innervation of the larynx.

The external branch runs downward and forward on the external surface of the inferior constrictor muscle and passes deep to the insertion of the sternothyroid muscle to supply the oblique and vertical part of the cricothyroid muscle as the motor nerve.

## 2 The recurrent nerve

The recurrent nerve divides into two branches at the level of the 2nd tracheal ring. The one branch, which is called the ramus posterior pro-

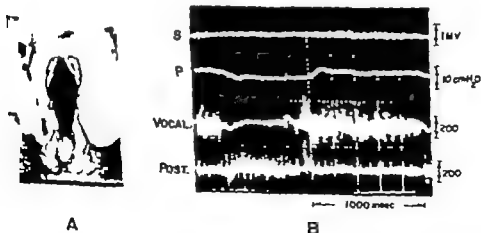


FIG. 2. (A) shows the larynx from the inspiratory phase of respiration. Dark or light and slightly lateral from the intermediate laryngeal opening is 4 mm wide. (B) the relationship of the subglottic pressure change and the action potential pattern of the laryngeal muscles. S: Sound; P: glottic pressure; Vocal EMG of the vocal muscle; Post EMG of the posterior cricoarytenoid muscle.

inserting a bipolar concentric needle electrode and subglottic pressures were measured by inserting a trocar into the trachea and attached to the cathode ray oscillograph via a strain gage type transducer

In order to compare vocal cord movement at a time of respiration phonation and deglutition with that induced by electrical stimulation of the laryngeal nerves, the experiments were first performed under normal innervated state and three observations were made in respiration phonation, and deglutition

For the nerve stimulation experiments of the superior and recurrent laryngeal nerves, the trachea was sectioned at the level of the 3rd ring to prevent passive movement of the vocal cords by respiratory air current. The internal branch of the superior laryngeal nerve was bilaterally sectioned at its entrance into the thyroid membrane and the external branch of the superior laryngeal nerves and the recurrent nerves were carefully isolated and divided approximately 5 cm away from their entrance into the larynx. Since the inferior constrictor muscle has some effect on vocal cord movement (Arnold 1961 Hiroto 1966 Levit *et al* 1965) the nerve branches distributed to the inferior constrictor muscles were transected

In the first part of the stimulation experiments, peripheral stumps of the external branch of the superior laryngeal nerves and the recurrent nerves were electrically stimulated

In the second part of the stimulation experiments, the single nerve branch to each individual muscle was stimulated. The external branch of the superior laryngeal nerve and the recurrent nerve were pursued to their peripheral fibers and divided at their diverging portions of the nerve branches distributed to each intrinsic laryngeal muscle and electrical stimulation was applied to each nerve branch individually or simultaneously

The stimulus was produced by a stimulator with coupled stimulus isolation unit (Grass Instrument Co) delivered to nerves by bipolar shielded silver wire electrodes at 3 mm polar distance. Stimulus voltage ranged 0.1 to 10 volts (threshold voltage was 0.3 volts in average) and stimulus frequency varied from 1/sec to 100/sec with square wave pulses of 0.1 millisecond duration

## RESULTS

### *A Innervation of the Larynx*

#### *1 The superior laryngeal nerve (Fig 1)*

The superior laryngeal nerve divides into an internal and an external branch. The internal branch subdivides into two branches immediately after entering through the thyrohyoid membrane. One branch is distributed to the epiglottis and the other descends to make the anastomosis with the posterior ramus of the recurrent nerve in addition to its laryngeal and pharyngeal distribution as the sensory nerve

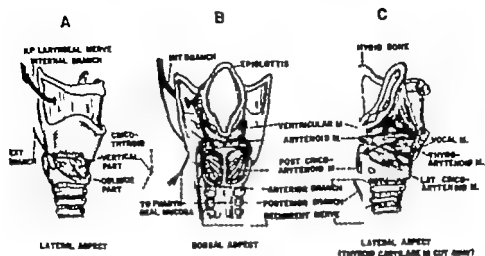


FIG. 1. This figure shows the innervation of the canine larynx.

The external branch runs downward and forward on the external surface of the inferior constrictor muscle and passes deep to the insertion of the sternothyroid muscle to supply the oblique and vertical part of the cricothyroid muscle as the motor nerve.

## 2. The recurrent nerve

The recurrent nerve divides into two branches at the level of the 2nd trachea ring. The one branch, which is called the ramus posterior pro-

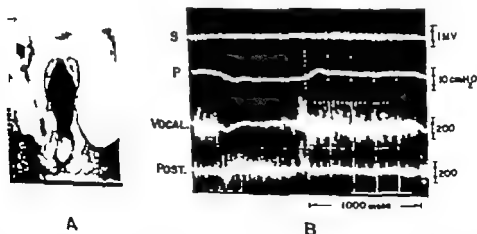


FIG. 2. (A) shows the laryngeal cast in the inspiratory phase of relaxed expiration. Both vocal cords are in slightly lateral from the intermediate line. Glottal opening is 6 mm. (B) shows relationship of the subglottic pressure change and the action potential pattern of the laryngeal muscles. S Sound; P subglottic pressure; Vocal EMG of the vocal muscle; Post EMG of the posterior cricoarytenoid muscle.

gresses in a posterior lateral direction and connects with the internal branch of the superior laryngeal nerve. The other called the ramus anterior proceeds in an anterior internal direction and divides into the nerve branches to the posterior cricoarytenoid muscle, the arytenoid and ventricularis muscle, the lateral cricoarytenoid muscle and the thyroarytenoid muscle (external thyroarytenoid and vocal muscle)

## *B Normal Vocal Cord Movement during Respiration Phonation and Deglutition*

### *1 Respiration (Fig 2)*

Both vocal cords are in the intermediate position during quiet respiration however the glottis becomes slightly wider during inspiration (Fig 2 A) and slightly narrower during expiration. Electromyogram shows that the abducting posterior cricoarytenoid muscle is more active during inspiration decreasing the subglottic pressure, while the adductors increase their activities with each expiratory cycle. The electrical discharge of the muscle starts to fire before onset of each respiration (Fig 2 B)

### *2 Phonation (Fig 3)*

Fig 3 A illustrates a position of the vocal cords at a time of phonation (whine) both vocal cords take the median and elongated position. Electromyogram showed considerable discharges in the adductor muscles and the cricothyroid muscle as compared with activity at the time of respiration. There are time delays between the onset of the muscle action potential the starting point of intratracheal pressure development and the initial sound at the beginning of phonation. The cricothyroid muscle begins activity earlier than that of the adductors (Fig 3 B)

### *3 Deglutition (Fig 4)*

The closure of the glottis begins with the anterior portion and proceeds posteriorly and the arytenoid cartilages are tightly pressed against the epiglottis (Fig 4 A) and finally sphincteric closure of the glottis results. The adductor muscles show marked activity during glottic closure phase corresponding to negative value of the subglottic pressure and activity of the cricothyroid muscle ceases at this time and reappears during glottal opening phase of deglutition (Fig 4 B)

## *C. Vocal Cord Movement Induced by Electrical Stimulation of the Laryngeal Nerves*

### *I Control position*

Fig 5 A shows the position of the vocal cords when all of the laryngeal nerves were cut. All of the intrinsic laryngeal muscle became atonic and

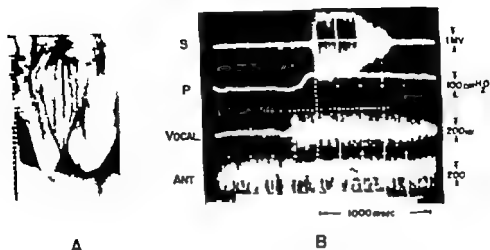


FIG. 3. (A) show the laryngeal film at time of phonation (whi). Both vocal cords take the median position and long to about 5 mm more compared with respiration. Scale mm. (B) show the relationship between the subglottic pressure change and the action potential pattern of the laryngeal muscles with phonation (hiss). Action potential of the vocal muscle is at 200 msec earlier than the beginning of the subglottic tone and 80 msec earlier than the rising point of subglottic pressure. Note that the cricothyroid muscle (tensor) triggers activity earlier than that of the vocal muscle (adductor).

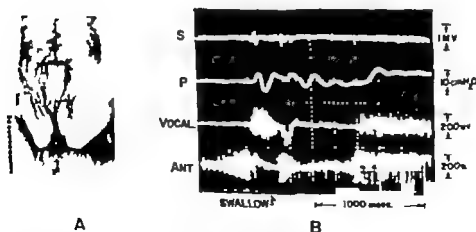


FIG. 4. (A) show the laryngeal film at time of deglutition (just before laryngeal sphincter closure of the glottis). (B) show relationship of the subglottic pressure change and the action potential pattern of the laryngeal muscles. S, subglottic pressure; Vocal EMG of vocal muscle; ANT EMG of cricothyroid muscle.



the vocal cords assumed the so-called intermediate position, one between the lateral and midline positions.

## II *Electrical stimulation of the external branch of the superior laryngeal nerve*

Fig 5 B demonstrates the position of the vocal cords when both external branches of the superior laryngeal nerves were stimulated with a frequency of 30/sec and an intensity of 1 volt. Both vocal cords became elongated slightly adducted and narrowing the glottis; however the vocal cords did not assume the median position even though the frequency and intensity of stimulation were increased. This indicates that more adduction as well as elongation of the vocal cords can be obtained by cricothyroid contraction. This position of the vocal cords should be referred to as the paramedian position.

Upon unilateral stimulation (Figs 5 C and 5 D) the vocal cord of the stimulated side was elongated and the posterior glottal commissure rotated to the opposite side showing homolateral adduction of the vocal cord with retraction of the arytenoid cartilage.

When the nerve branch distributed to the oblique part (Fig 5 E) of the right cricothyroid muscle was stimulated the posterior glottal commissure deviated to the opposite side as a result of rotation of the anterior aspect of the cricoid to the side of stimulation and when the nerve branch distributed to the vertical part (Figs 5 F and 1 A) of the right cricothyroid muscle was stimulated the vocal cord of the stimulated side was elongated and adducted.

## III *Electrical stimulation of the recurrent nerve*

1 Effect of stimulus frequency change (Fig 6) Electrical stimulation was applied on both recurrent nerve stumps with constant intensity of 1 volt and the frequency was changed 1 to 100/sec. Although flicker movement of the vocal cords occurred corresponding to each stimulus during low frequency stimulation this flicker movement shifted to smooth abduction of the vocal cords at a frequency of 13-15/sec and the glottis opened wider as stimulus frequency increased and assumed the lateral position when the frequency reached 20/sec.

If the frequency raised higher than 30/sec, steadier adduction of the vocal cords started anteriorly assuming the paramedian position at the frequency of 30-35/sec and sphincteric closure of the glottis similar to that observed during deglutition occurred. Complete closure of the glottis was achieved at the stimulus frequency of 60-70/sec.

2 Effect of stimulus intensity change (Fig 7) When the stimulus intensity was changed from 1 to 10 volts at the constant frequency of 20/sec the glottal opening became wider as the stimulus intensity increased and the vocal cords abducted to the extreme lateral position at the stimulus



FIG. 5 Fig 5 shows various laryngeal views when the terminal branches of the superior laryngeal nerves are electrically stimulated. Stimulating voltage = 10 V frequency 30 sec. pulse duration = 0.1 msec. (A) Control. The vocal cord takes the intermediate position. Glottal opening is about 3 mm in width. (B) Bilateral. The terminal branches are stimulated bilaterally. Both vocal cords elongated and abducted to the paramedian position (3 mm glottal width). (C) Right, (D) left, show the lateral view at time of unilateral stimulation of the terminal branch. (E) R-Oblique. The right branch distributed to the oblique part of the right cricothyroid muscle. Individually stimulated. The posterior glottal commissure deviated to the opposite side. (F) R-V. The right branch distributed to the vertical part of the right cricothyroid muscle and individually stimulated. Elevation, elongation and adduction of the right vocal cord resulted.

CONTROL 20/sec. 30/sec 40/sec 50/sec 60/sec



FIG. 6 Fig 6 shows different laryngeal views when bilateral recurrent nerves are stimulated with various frequencies and constant interval of 1 sec. Control shows the intermediate position of the vocal cords (3 mm glottal width). The vocal cords abduct to the lateral position at the stimulus frequency of 20 sec (7 mm glottal width) and by increasing stimulus frequency to more than 30 sec, closure of the glottis occurs from the lateral aspect and the arytenoid parts pressing to the epiglottis, glottal opening becomes smaller. Stimulus frequency increases (40-60 sec). Complete closure of the glottis occurs when the stimulus frequency reaches 60 sec.

CONTROL A) 20/sec. B) 40/sec.



FIG. 7 Fig 7 shows different glottal views upon the stimulus intensity changes. (A) Stimulus intensity increased to constant frequency of 20 sec. Glottal width 7 mm at 1 volt, 8 mm at 2 volts and 9 mm at 3 V (extreme lateral position). (B) Stimulus intensity increased to constant frequency of 40/sec. Glottal opening became narrower as the stimulus strength increased.

the vocal cords assumed the so-called intermediate position one between the lateral and midline positions

## *II Electrical stimulation of the external branch of the superior laryngeal nerve*

Fig 5 B demonstrates the position of the vocal cords when both external branches of the superior laryngeal nerves were stimulated with a frequency of 30/sec and an intensity of 1 volt. Both vocal cords became elongated slightly adducted and narrowing the glottis; however the vocal cords did not assume the median position even though the frequency and intensity of stimulation were increased. This indicates that more adduction as well as elongation of the vocal cords can be obtained by cricothyroid contraction. This position of the vocal cords should be referred to as the paramedian position.

Upon unilateral stimulation (Figs 5 C and 5 D) the vocal cord of the stimulated side was elongated and the posterior glottal commissure rotated to the opposite side showing homolateral adduction of the vocal cord with retraction of the arytenoid cartilage.

When the nerve branch distributed to the oblique part (Fig 5 E) of the right cricothyroid muscle was stimulated, the posterior glottal commissure deviated to the opposite side as a result of rotation of the anterior aspect of the cricoid to the side of stimulation and when the nerve branch distributed to the vertical part (Figs 5 F and 1 A) of the right cricothyroid muscle was stimulated, the vocal cord of the stimulated side was elongated and adducted.

## *III Electrical stimulation of the recurrent nerve*

1 Effect of stimulus frequency change (Fig 6) Electrical stimulation was applied on both recurrent nerve stumps with constant intensity of 1 volt and the frequency was changed 1 to 100/sec. Although flicker movement of the vocal cords occurred corresponding to each stimulus during low frequency stimulation, this flicker movement shifted to smooth abduction of the vocal cords at a frequency of 13-15/sec and the glottis opened wider as stimulus frequency increased and assumed the lateral position when the frequency reached 20/sec.

If the frequency raised higher than 30/sec, steadier adduction of the vocal cords started anteriorly assuming the paramedian position at the frequency of 30-35/sec and sphincteric closure of the glottis similar to that observed during deglutition occurred. Complete closure of the glottis was achieved at the stimulus frequency of 60-70/sec.

2 Effect of stimulus intensity change (Fig 7) When the stimulus intensity was changed from 1 to 10 volts at the constant frequency of 20/sec the glottal opening became wider as the stimulus intensity increased and the vocal cords abducted to the extreme lateral position at the stimulus



Fig. 5. Fig. 5 shows various laryngeal views when the external branches of the superior laryngeal nerves are electrically stimulated. Stimulation intensity 1 volt, frequency 20/sec, and duration = 0.1 msec. (A) Control. The vocal cord takes the intermediate position. Glottal opening is about 5 mm in width. (B) Bilateral. The terminal branches stimulated bilaterally. Both vocal cords long and abducted to the paramedian position (3 mm glottal width). (C) Right and (D) left show the laryngeal view at time of unilateral stimulation of the external branch. (E) R-Oblique. The nerve branch distributed to the oblique part of the right cricothyroid muscle is individually stimulated. The posterior glottal commissure deviated to the opposite side. (F) R-Ventral. The nerve branch distributed to the vertical part of the right cricothyroid muscle is individually stimulated. When stimulation and adduction of the right vocal cord is noted.



Fig. 6. Fig. 6 shows different laryngeal views when bilateral recurrent nerves are stimulated with various frequencies and constant intensity of 1 volt. Control shows the intermediate position of the vocal cord (8 mm glottal width). The vocal cord abducted to the lateral position. The stimulation frequency of 20/sec (7 mm glottal width) and by increasing stimulation frequency more than 30/sec closure of the glottis occurs from the anterior aspect and the arytenoid parts pressing against the epiglottis, glottal opening becomes smaller. Stimulation frequency increases (40-60/sec). Complete closure of the glottis occurs when the stimulation frequency reaches 60/sec.



Fig. 7. Fig. 7 shows different glottal views upon the stimulation intensity change. (A) Stimulus intensity increased to constant frequency of 20/sec. Glottal width is 7 mm at 1 V, 8 mm at 2 V and 9 mm at 3 volts (extreme lateral position). (B) Stimulation intensity increased to constant frequency of 40/sec. Glottal opening became narrow. The stimulus change increased.

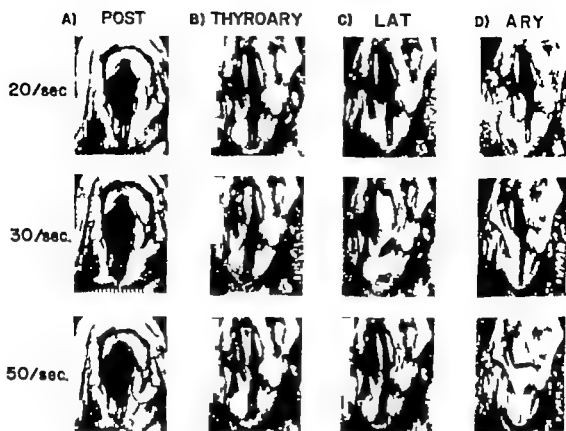


FIG. 8 The recurrent nerve branches distributed to each intrinsic laryngeal muscle on the left side were stimulated with various frequencies and constant intensity of 1 volt. (A) POST The nerve branches to the posterior cricoarytenoid muscle on the left side individually stimulated. The vocal cord on the stimulated side abducted to a lateral position at the frequency of 20/sec and abduction of the vocal cord took place with stimulus frequency increased. Laternal displacement and deflection of the arytenoid part is obvious. (B) (C) and (D) The nerve branches distributed to the left thyroarytenoid muscle (B), lateral cricoarytenoid muscle (C), and cricothyroid muscle (D) are stimulated. The anterior portion (B), middle portion (C), and posterior portion (D) of the left vocal cord adduct by increasing the stimulus frequency. Slight abduction of the stimulus frequency of 20/sec and remarkable adduction at the stimulus frequency of more than 30/sec were noted. Internal displacement and deflection of the arytenoid part was invariably observed.

intensity of 5 volts. If the frequency was kept constant at 40/sec, adduction of the vocal cords always took place as stimulus intensity increased and complete closure of the glottis was observed at the stimulus intensity of 8 volts.

#### IV Stimulation of the individual branches of the recurrent nerve distributed to each intrinsic laryngeal muscle

To explore the different glottal movement according to the frequency of the electrical stimulation of the recurrent nerves, stimulation was applied to the nerve branches distributed to each intrinsic laryngeal muscle.

1 Stimulation of the nerve branch distributed to the left posterior cricoarytenoid muscle (Fig. 8 A)

When the nerve branch distributed to the left posterior cricoarytenoid muscle was stimulated individually the left vocal cord abducted by increasing the stimulus frequency and assumed the extreme lateral position at a frequency of 20/sec and did not adduct by increasing the stimulus frequency higher than 30/sec.

2 Stimulation of the nerve branch distributed to the left thyroarytenoid muscle (including vocalis muscle) (Fig. 8 B)

Adduction of the anterior part and shortening of the vocal cord on the stimulated side resulted. Slight adduction of the anterior part of the vocal cord at a stimulus frequency of 20/sec and strong adduction with the stimulus frequency higher than 30/sec were observed.

3 Stimulation of the nerve branch distributed to the left lateral cricoarytenoid muscle (Fig. 8 C)

The middle part of the left vocal cord adducted slightly at a frequency of 20/sec and further adduction took place by increasing the stimulus frequency higher than 30/sec.

4 Stimulation of the nerve branch distributed to the left arytenoid muscle (including ventricularis muscle) (Fig. 8 D)

The posterior part of the left vocal cord adducted slightly at a stimulus frequency of 20/sec, and further adduction was followed by increasing the stimulus frequency higher than 30/sec, although there remained a slight crevice at the anterior part of the glottis. Abduction of the vocal cord was not observed.

#### *5 Simultaneous stimulation of the nerve branches distributed*

*1 the posterior cricoarytenoid muscle (abductor) and each adductor muscle (Fig. 9)*

1 Simultaneous stimulation of the nerve branches distributed to the right posterior cricoarytenoid and thyroarytenoid muscles (including vocalis muscle) (Fig. 9 A)

Although the right vocal cord abducted to the lateral position at a frequency of 20/sec adduction of the anterior part of the right vocal cord was followed by increasing the stimulus frequency higher than 30/sec.

2 Simultaneous stimulation of the nerve branch distributed to the right posterior cricoarytenoid and lateral cricoarytenoid muscles (Fig. 9 B)

There also occurred abduction of the right vocal cord at a frequency of 20/sec and slight adduction of the middle part of the right vocal cord took place by further increasing the stimulus frequency to over 30/sec.

3 Simultaneous stimulation of the right posterior cricoarytenoid and arytenoid muscles (including ventricularis muscle) (Fig. 9 C)

Abduction of the right vocal cord was observed at a stimulus frequency of 20/sec and adduction of the posterior part of the right vocal cord occurred as stimulus frequency increased more than 30/sec.

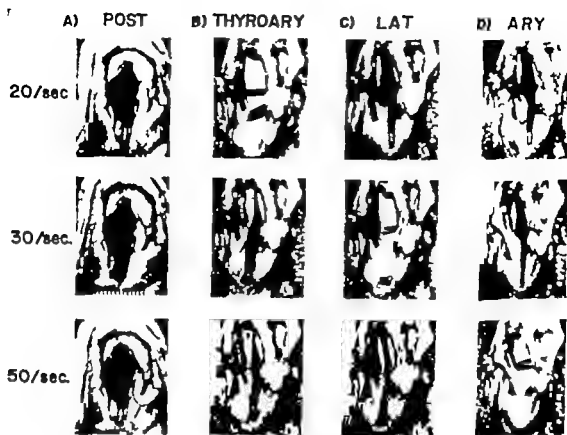


FIG. 8 The recurrent nerve branches distributed to each intrinsic laryngeal muscle in the left side were stimulated with various frequencies and at constant intensity of 1 volt (A) Post: The nerve branch to the posterior cricoarytenoid muscle in the left side is individually stimulated. The vocal cord in the stimulated side adducted to a lateral position at the frequency of 20/sec and adduction of the vocal cord took place as the stimulus frequency increased. Lateral displacement and deflection of the arytenoid part is obvious. (B) (C) and (D): The nerve branches distributed to the left thyroarytenoid muscle (B) lateral cricoarytenoid muscle (C) and arytenoid muscle (D) are stimulated. The anterior portion (B) middle portion (C) and posterior portion (D) of the left vocal cord adduct by increasing the stimulus frequency. Slight deflection of the stimulus frequency of 20/sec and remarkable deflection at the stimulus frequency of more than 30/sec were noted. Internal displacement and deflection of the arytenoid part are in all observed.

**Intensity of 5 volts** If the frequency was kept constant at 40/sec adduction of the vocal cords always took place as stimulus intensity increased and complete closure of the glottis was observed at the stimulus intensity of 8 volts.

#### IV. Stimulation of the individual branches of the recurrent nerve distributed to each intrinsic laryngeal muscle

To explore the different glottal movement according to the frequency of the electrical stimulation of the recurrent nerves, stimulation was applied to the nerve branches distributed to each intrinsic laryngeal muscle.

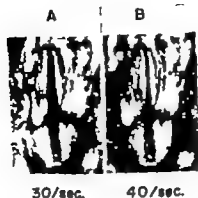


FIG. 10. Upon bilateral stimulation, both vocal cords elongated and adducted to the paramedian position at the frequency of 30/sec (A) and further adduction was followed by increasing stimulus frequency more than 40/sec (B).

*VL. Simultaneous stimulation of the external branch of the superior laryngeal nerve and all adductor nerve branches of the recurrent nerve (Fig. 10)*

To obtain the vocal cord position similar to the phonatory position, electrical stimulation was applied to bilateral external branches of the superior laryngeal nerves and bilateral recurrent nerve branches distributed to all adductor muscle simultaneously. Elongation and adduction to the paramedian position of the vocal cords were observed at a frequency of 23-30/sec (Fig. 10 A) and further adduction was followed by increasing stimulus frequency (Fig. 10 B) and complete adduction to the median position was achieved at a stimulus frequency of 60/sec.

# DISCUSSION

From the electromyographic standpoint, excitation of a few motor units evokes a slight contraction of the muscle and when many motor units discharge vigorous contraction of the muscle results. Respiration for instance is represented by slight contraction of the intrinsic laryngeal muscles, phonation by moderate, and the act of deglutition is one of marked contraction.

During quiet respiration the vocal cords are in constant pendulous motion from their neutral or resting position (intermediate line). In deep respiration, the lateral movement of the cords during inspiration and internal movement during expiration become progressively greater as respiration becomes deeper and more forceful (Presman & Kelemen, 1955).

Electrical stimulation of the recurrent nerves with a low frequency around 10/sec showed vocal cord contraction corresponding to each stimulus staying within the intermediate line which is similar to the position



A) THYROARY  
& POST

## B) LAT &amp; POST

## C) ARY &amp; POST

10/sec



20/sec



30/sec



50/sec



FIG. 11. The nerves branches distributed to the right posterior cricoarytenoid muscle (abductor) and adductor muscle in the right larynx ((A) thyroarytenoid muscle (B) lateral cricoarytenoid muscle (C) aryepiglottic muscle) were stimulated simultaneously.

The vocal cord of the stimulated larynx adducted lightly at the frequency of 10/sec and marked adduction at 20/sec (A) (B) and (C) were adducted. At the frequency of 30/sec and 50/sec, the vocal cord adducted. At the frequency of 50/sec, the vocal cord adducted. At the frequency of 50/sec, the vocal cord adducted. At the frequency of 50/sec, the vocal cord adducted.

ment of the vocal cords by homorhythmic impulses conducted through the recurrent nerve. As expected, our results do not support this theory because (1) discharge frequencies of the single motor units in the vocal muscle during phonation did not coincide with vocal pitch, and (2) flicker movement of the vocal cords which was induced by electrical stimulation of the laryngeal nerves cannot be observed when the stimulus frequency increased more than 15/sec.

During deglutition, the action potentials of the cricothyroid muscle ceased at the glottic closure phase of deglutition while the adductors show a vigorous activity. On the other hand, complete closure of the glottis similar to that of swallowing was achieved with a high frequency stimulation of both recurrent nerves. These results reveal that the cricothyroid muscle does not play the important role for the glottic closure during deglutition.

With reference to the mechanism of vocal cord elongation and auxiliary adduction by cricothyroid contraction with stimulation experiments, it elevates the anterior portion of the cricoid ring towards the thyroid cartilage narrowing the cricothyroid distance and elongating the thyroarytenoid distance. Consequently the vocal cords are stretched and tensed. This increased tension of the vocal cords moves the vocal process of the arytenoid cartilage medially adducting the vocal cords from the intermediate to the paramedian position.

Unilateral cricothyroid contraction induces homolateral elongation and adduction of the vocal cord with deviation of the posterior glottal commissure to the opposite side. From Figs. 5 E and 5 F elongation and adduction of the vocal cord is mainly due to contraction of the vertical part, whereas opposite deviation of the posterior glottal commissure as a result of rotation of the anterior aspect of the cricoid ring to the side of stimulation is caused by the backward pull of the oblique part of the cricothyroid on the stimulated side. This means that in case of unilateral paralysis, the posterior commissure is deviated to the side of paralysis.

There are some reports which observed vocal cord movement at a time of recurrent nerve stimulation. Seymour & Henry (1954) observed in the cat larynx that small voltages produced adduction movement of the glottis and with increasing strength of stimulus, an adductor "flick" could be observed followed by an active abductor movement.

Mortagh & Campbell (1941) also obtained only adduction in similar experiment on the goat's larynx. Williams (1951) observed only adduction with minimal stimuli on human recurrent nerves.

Capps (1958) observed the following results in human larynx. Recurrent nerve stimulation at 10 volts and 8 pulses/sec induced adductor flicks. Stimulation at 10 volt and 25 pulses/sec induced steadier adduction and stimulation of 50 volts and 25 pulses/sec produced abduction. These results reveal that the vocal cords showed a different movement with increasing stimuli (voltage) strength at constant frequency.

From our observation, while alteration of the stimulus strength showed

of quiet respiration. When the stimulus frequency reached 20/sec, the vocal cords assumed the lateral position which is similar to the deep inspiratory position. On the other hand, when the external branch of the superior laryngeal nerve was bilaterally stimulated (Fig 5 B) at a frequency of 25–30/sec, the vocal cords assumed the paramedian position similar to the deep expiratory position. These results are in close agreement with the findings of Nakamura *et al* (1958) that is, during respiration many of the continuously discharging single motor units of the laryngeal muscle increased their frequency from the range of 5–10 impulses/sec during rest, to the range of 10–20 impulses/sec during contraction and sometimes to the range of 50–60/sec.

During phonation there exists the latent time between the first visible appearance of the action potentials, the beginning of subglottic pressure development and the subsequent audible onset of phonal function. During this latent time, the laryngeal muscles bring the cords into proper position and tension for each vocal performance before expiratory air stream begins to set them into vibratory motion. Since low pitch voice production within average speech range (chest register) is due to repeated opening and closing movement of the vocal cords, usual speaking voice requires little cricothyroid activity. On the other hand, in higher pitch voice production (head register) the vocal cords elongated and strained and vibration is observed only along the inner edge of the vocal folds (Kirikae, 1943; Luchsinger & Arnold, 1949).

Whine is a high pitch tone and corresponds to the head register and action potential of the cricothyroid muscle fired before the adductors. Concerning whine, tension of the vocal cords takes place first and then adduction to the phonatory position occurs. This same movement of the vocal cords was observed at a time of simultaneous stimulation of extrinsic superior laryngeal nerves and all adductor nerve branches of the recurrent nerves (Fig 10). The tension and adduction to the paramedian position of the vocal cords were observed at the stimulus frequency of 30/sec and then further adduction to the median position was achieved with frequencies higher than 40/sec.

The discharge frequency of single motor units of the adductor and tensor muscles during phonation increased when compared with that during respiration. Katsuki (1950) reported that with rising pitch the discharge frequency of the cricothyroid muscle increased until 20–40 impulses per second for the highest tones of falsetto voice. Faaborg Andersen (1957) described a similar discharge frequency of a single motor unit ranging from 3 to about 30 per second. Urata (1960) reported maximal discharge frequency of single motor units in the vocal muscle was 60/sec during phonation. These discharge frequencies are of course much lower than the vibratory frequencies in cycle of the audible tone.

According to Huxson's neurochronaxic theory (1956) the frequency of vibration of the vocal cords at a given pitch of voice is due to active move-

ment of the vocal cords by homorhythmic impulses conducted through the recurrent nerve. As expected, our results do not support this theory because (1) discharge frequencies of the single motor units in the vocal muscle during phonation did not coincide with vocal pitch, and (2) flicker movement of the vocal cords which was induced by electrical stimulation of the laryngeal nerves cannot be observed when the stimulus frequency increased more than 15/sec.

During deglutition, the action potentials of the cricothyroid muscle ceased at the glottic closure phase of deglutition while the adductors show a vigorous activity. On the other hand, complete closure of the glottis similar to that of swallowing was achieved with a high frequency stimulation of both recurrent nerves. These results reveal that the cricothyroid muscle does not play the important role for the glottic closure during deglutition.

With reference to the mechanism of vocal cord elongation and auxiliary adduction by cricothyroid contraction with stimulation experiments, it elevates the anterior portion of the cricoid ring towards the thyroid cartilage narrowing the cricothyroid distance and elongating the thyroarytenoid distance. Consequently the vocal cords are stretched and tensed. This increased tension of the vocal cords moves the vocal process of the arytenoid cartilage medially adducting the vocal cords from the intermediate to the paramedian position.

Unilateral cricothyroid contraction induces homolateral elongation and adduction of the vocal cord with deviation of the posterior glottal commissure to the opposite side. From Figs 5 E and 5 F elongation and adduction of the vocal cord is mainly due to contraction of the vertical part, whereas opposite deviation of the posterior glottal commissure as a result of rotation of the anterior aspect of the cricoid ring to the side of stimulation is caused by the backward pull of the oblique part of the cricothyroid on the stimulated side. This means that in case of unilateral paralysis, the posterior commissure is deviated to the side of paralysis.

There are some reports which observed vocal cord movement at a time of recurrent nerve stimulation. Seymour & Henry (1954) observed in the cat larynx that small voltages produced adduction movement of the glottis and with increasing strength of stimulus, an adductor "flick" could be observed followed by an active abductor movement.

Mortagh & Campbell (1945) also obtained only adduction in similar experiments on the goat's larynx. Williams (1951) observed only adduction with minimal stimuli on human recurrent nerves.

Capps (1938) observed the following results in human larynx. Recurrent nerve stimulation at 10 volts and 6 pulses/sec induced adductor flicks. Stimulation at 10 volts and 25 pulses/sec induced steadier adduction and stimulation of 50 volts and 25 pulses/sec produced abduction. These results reveal that the vocal cords showed a different movement with increasing stimulus (voltage) strength at constant frequency.

From our observation, while alternation of the stimulus strength showed

different glottal movement, by contrast, the effect of glottal movements was very dramatic with constant stimulus strength but increasing frequency change (Figs 6 and 7)

Looking at the different movement of the vocal cords depending upon the frequencies of the recurrent nerve stimulation if the nerve branch distributed to the posterior cricoarytenoid muscle was stimulated individually the vocal cords abducted to the extreme lateral position at a frequency of 20/sec and adduction of the vocal cords can not be seen even though the stimulus frequency increased higher than 30/sec.

On the other hand when the nerve branches distributed to each adductor muscle was individually stimulated, only adduction of the vocal cords was observed i.e., slight adduction of the vocal cords occurred at the frequency of around 20/sec and further adduction was followed by increasing stimulus frequency more than 30/sec.

Further if the stimulation was applied to the nerve branches distributed to the posterior cricoarytenoid muscle and each individual adductor muscle simultaneously abduction of the vocal cords occurred at a frequency of 20/sec and adduction of the vocal cords invariably took place by increasing the stimulus frequency more than 30/sec

Thus the posterior cricoarytenoid muscle has a tendency to respond to the lower frequency impulses, when compared with the adductor muscles and that of the cricothyroid muscle is between that of the abductor and adductors

These results show that there are different impulse frequencies to induce the effective contraction of each abductor and adductor muscle, that is from a viewpoint of vocal cord movement, maximum tension of the posterior cricoarytenoid muscle occurs at a frequency of 20/sec, while higher frequencies are needed to achieve maximum tension of the adductors. In other words, the adductor muscles have high frequency characteristics compared with the abductor muscles. The larynx opens with lower frequency stimulus (fewer motor units discharge) or acts as a sphincteric valve with higher frequency discharges (many motor units discharge)

## CONCLUSION

1 During quiet respiration, the vocal cords are slightly abducted with inspiration and slightly adducted with expiration about the intermediate line. Electromyogram showed action potential of the abductor muscles is more active during inspiration while the adductors increase their activity during expiration

2. During phonation (whine) the vocal cords are elongated and assumed the median position. Electromyogram showed considerable discharge in the cricothyroid muscle (Tensor) and the adductors. The cricothyroid muscle triggers activity earlier than that of the adductors.

3 During deglutition, both vocal cords adduct from the anterior aspect and shorten and the arytenoid part is pressed against the epiglottis and strong sphincteric closure of the glottis occurs. The adductors showed strong electrical discharge during glottal closing phase of deglutition, while the cricothyroid muscle ceases electrical activity at this time

4 Bilateral stimulation of the external branch of the superior laryngeal nerve induced elongation and adduction of the vocal cords to the paramedian position by increasing stimulus frequency to 25-30/sec.

5 Unilateral stimulation of the external branch of the superior laryngeal nerve induced deviation of the posterior glottal commissure to the opposite side

6 Unilateral stimulation of the nerve branch to the vertical part of the cricothyroid muscle induced homolateral elongation and adduction of the vocal cord.

Unilateral stimulation of the nerve branch to the oblique part of the cricothyroid induced deviation of the posterior glottal commissure to the opposite side

8 Bilateral recurrent nerve stimulation induced abduction of the vocal cords to the lateral position at a frequency of 20/sec. Adduction of the vocal cords took place by increasing stimulus frequency more than 30/sec and complete closure of the glottis was achieved at a stimulus frequency of 60-70/sec.

9 Increase of the stimulus strength at constant frequency of 20/sec induced abduction of the vocal cords to the extreme lateral position, and increase of the stimulus strength at constant frequency of 40/sec induced glottal closure

10 Individual stimulation of the nerve branch to the posterior crico-arytenoid induced only abduction and assumed the extreme lateral position at a frequency of 20/sec.

11 Individual stimulation of the nerve branch distributed to each adductor muscle induced slight adduction of the vocal cords at a frequency of 20/sec and strong adduction with the stimulus frequency more than 30/sec

12 Simultaneous stimulation of the nerve branch distributed to the abductor and each adductor muscle induced abduction of the vocal cords at a stimulus frequency of 20/sec and adduction of the vocal cords invariably took place as stimulus frequency increased more than 30/sec.

13 Simultaneous stimulation of the external branch of the superior laryngeal nerve and all nerve branches distributed to the adductors induced vocal cord elongation and adduction to the paramedian position at a frequency of 25-30/sec and further adduction to the median position occurred with the stimulus frequency more than 40/sec.

## RESUME

Nous avons étudié les mouvements des cordes vocales chez le chien pendant la respiration et la phonation (hurlement). Nous avons déterminé les fréquences de stimulation pour l'adduction et la fermeture de la supraglotte. Nous avons comparé une greffe musculo nerveuse du nerf larynge récurrent et la réanastomose d'autres portions du même nerf.

## ZUSAMMENFASSUNG

Die vorliegenden Untersuchungen betreffen die Stimmbandbewegungen von Hunden während Atmung und während Phonation (Winseln). Das Verhältnis von Reizfrequenz zu Adduktion und Verschluss der Supraglottis wurde geprüft. Ferner wurden Untersuchungen von gestielten Nerv Muskeltransplantaten des Nervus recurrens und Reanastomosen der übrigen Anteile desselben verglichen.

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## DISCUSSION

F. Brunetti (J. Stille) vs. tout M. Ogura pour l'intéressante documentation scientifique qu'il a présentée et demand s'il n'y a pas aussi des expériences électromyographiques avec des curares, comme on a déjà fait dans la Clinique ORL de Turin pour étudier le comportement très différent entre muscles et phonations vers les phénomènes de dépolarisation et de repolarisation provoqués par ces substances pharmacologiques.

A. Leskiewicz: As for the paramedian position of the vocal cord, I would like to mention that Ant. Jura (L. von Poland) in 1906 was the first who had theoretically suggested that this position is due not only to a lesion of the recurrent nerve of the sick concerned but that the superior laryngeal nerve is to be contemporary involved. In 1924 Gust. Hofer (Vienna) had experimentally on animals proved that the same position of the vocal cord is due to lesion of the recurrent nerve and the section of the superior laryngeal nerve simultaneously.

M. Barr II: H. M. Ogura noticed in his experiments on deglutition movements of the epiglottis.

J. H. Ogura (Reply) to Mr. Brun III: We did not study vocal cord movement and effect of drugs.

to Mr. Leskiewicz: I am familiar with the statement that a lateral position is due to injury of the recurrent laryngeal nerve and division of the superior laryngeal nerve. These studies were made in animals to gain insight into the problem of



## RESUME

Nous avons étudié les mouvements des cordes vocales chez le chien pendant la respiration et la phonation (hurlement). Nous avons déterminé les fréquences de stimulation pour l'adduction et la fermeture de la supraglotte. Nous avons comparé une greffe musculo-nerveuse du nerf larynge récurrent et la réanastomose d'autres portions du même nerf.

## ZUSAMMENFASSUNG

Die vorliegenden Untersuchungen betreffen die Stimmbandbewegungen von Hunden während Atmung und während Phonation (Winseln). Das Verhältnis von Reizfrequenz zu Adduktion und Verschluss der Supraglottis wurde geprüft. Ferner wurden Untersuchungen von gestielten Nerv-Muskeltransplantaten des Nervus recurrens und Reanastomosen der übrigen Anteile desselben verglichen.

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## COMPARISON BETWEEN NEURAL AND PSYCHOPHYSICAL RECORDINGS OF TASTE STIMULATIONS

H. DIAMANT M.D.

*From the Department of Otorhinolaryngology, University of Umeå,  
Umeå, Sweden*

*In a series of experiments in man it is possible to show the very strong resemblance between the neural recordings established during operation and the preoperative findings at psychophysical stimulation.*

For many years, the former head of the Physiological Department of the Veterinary School in Stockholm, Professor Ingve Zotterman has done research on the sense of taste. His experiments started over forty years ago and he has continuously and consistently fulfilled his experiments in different ways to solve problems connected with taste.

The experiments were in the beginning performed on different animals, but at the end of the fifties Professor Zotterman tried, together with Doctor Ahlander of the Southern Hospital in Stockholm, to record from the chorda tympani in humans. The experiments were for different reasons, not successful, and were later transferred to the Karolinska Hospital where together with Professor Zotterman succeeded in making some recordings from the chorda tympani. These experiments were continued at the Ear Department of the Karolinska Hospital where there was a very well shielded room in which a series of recordings were taken from the chorda tympani.

It is fortunate that, by a freak of nature, impulses from the tongue to the brain pass in the chorda tympani through the middle-ear. Thanks to the very rapid development of middle-ear surgery, especially surgery for stapes and the oval window, the chorda tympani has become easily available for examination. In many cases the chorda tympani is an obstacle to the surgeon on his way to the stapes, and has to be cut. It seemed that patients did not have very much trouble from this divided chorda. Anyway they very seldom complained of this trouble and above all the troubles were so small in comparison with the very great gain in hearing that they did not mention them.

To be able to successfully record from the chorda tympani some condition must be fulfilled. First of all, one must have a very good electrically shielded room. Secondly, all the preoperative examinations of the taste of the patient has to be very thorough. Professor Zotterman has a lot of experience here. We have also used the experience of psychologists working with psychophysical examinations of taste. The third condition is, of course, that you have the ethical justification for these experiments. The patient who is operated upon will only have the operation-time prolonged

reinnervation in our experiments with replantation and transplantation of the larynx. Reinnervation will be important for maintenance of vasomotor tone as well as movement of the vocal cords. Thus we need information on frequency stimulus response of each nerve branch and vocal cord movements for our control study.

to Mr. Barretto: There was some posterior movement of the epiglottis but these observations were made through an anterior pharyngotomy approach which would make these findings less significant. Movement of the epiglottis can be nicely observed by cine-radiographic studies of deglutition and on phonation.

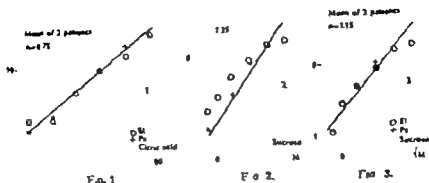


Fig. 1 Relation between taste responses (Pr) and electrical responses (El) for citric acid. Mean of 2 patients.

Fig. 2. See text.

Fig. 3 Relation between taste responses (Pr) and electrical responses (El) for sucrose. Mean of 2 patients.

When we did consider the results of the experiments it seemed that most of what we tried to prove had been achieved. But since then we have made a very thorough examination of what generally happens with patients who have their chorda tympani divided and we found that many of the patients in fact have more trouble than earlier investigators thought and even if the troubles in many cases are insignificant they are serious enough. You thus have to take these complications into consideration when you are performing the operation for stapes-surgery. That means that one must try to avoid damaging the chorda tympani and that experiments should be performed on undivided chorda tympani. Because of this, we have constructed a micro-manipulator with which it is possible to reach the chorda tympani and put a micro-electrode in it for direct recordings. In this way the recording will be taken from a very small strand of the nerve instead of from the whole nerve—if you are lucky. So far we are just at the beginning of this work, which is very tedious and will take a long time, but which we hope will get still better results than those we have obtained so far.

### RESUME

Des séries d'expériences chez l'homme la stimulation gustative nerveuse pendant l'opération a été comparée à la stimulation psychologique avant l'opération.

### ZUSAMMENFASSUNG

In einer Serie von Versuchen an Menschen kann man eine stark Gleichheit beobachten zwischen den neuralen Registrierungen, erhalten bei Operationen und den präoperativen Beobachtungen bei psychophysischer Reizung.

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one hour. We can keep the time down by good planning, so the trouble the patient will have is just the cut chorda which is something which will happen anyway in a lot of cases.

The early investigations gave valuable information about the relation between the strength of the gustatory stimulus and the recorded summated responses from the human chorda to various taste solutions. Working on human subjects offers the possibility of collecting information not only on the relationship between gustatory stimulus and the neural response but also on the relation between the neural and psychophysical responses.

When I left Stockholm for Umeå we could continue the research already begun, especially since we succeeded in putting up an electrically shielded metal-cage inside one of our operating theatres. We started the work with Docent Borg who is assisting professor in clinical psychology and who made the psychophysical investigations. That was the beginning of a series of experiments which were performed to make a comparison between the neural and psychophysical responses to gustatory stimuli.

During 1965-1966 we performed experiments in 18 cases. The results were very promising especially on two occasions, October 1965 and February 1966. The last experiments in August 1966 confirmed the results. The psychophysical examinations were performed two days before the operation using citric acid, NaCl and sucrose. The method of magnitude estimation was used. This method was introduced by Stevens and requires that the subjects can handle numbers and make quantitative estimations on the ratio level. In a pre-experiment all patients had to make estimations of surfaces of different sizes so that we could screen out those who obviously could not make magnitude estimations. The same stimuli and the same random order of presentation were used in the electrophysiological experiments. The stimuli were presented in pairs, the standard with one comparison stimulus. To test the method psychophysical experiments of the same kind using salt and citric acid were made on 14 young students. Straight lines may be adjusted to the values; it means that a power function may describe the relations. The Fechnerian log function does, however, better describe the variation in neural activity. If, as a first rough estimation, we describe both the neural and the psychophysical responses with power function we find an astonishingly good agreement. The exponent of the psychophysical function  $n_x = 0.5$  is the same as that of the neurophysiological function  $n_x = 0.5$ .

We succeeded in obtaining from 2 patients (I, J and S, P) subjective estimations as well as electrical responses to sucrose and citric acid. Fig. 1 shows the relative psychophysical and electrical responses to citric acid and they are plotted in a log-log diagram. Fig. 2 gives the relations for sucrose for 3 patients. Each point is the median of three observations in each series of tests on the same individual. How well the psychophysical functions follow the neural will be seen from Fig. 3 where the diagram gives the functions of the mean values obtained for two of the patients.

## ON THE IMPORTANCE OF TRACE ELEMENTS FOR MUCOSA OF UPPER AIR PASSAGES

A. ZAKRZEWSKI M.D

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Serum iron level was determined in 31 scleroma patients (20 previously cured with antibiotics, 2 requiring further treatment and 3 untreated). The determinations were performed in fasting patients and 3 and 6 hours after oral administration of 180 mg of ferric sulphate. In 20 of them the serum copper level was determined too. In 29 subjects the serum iron content was found to be under bottom norm, in 13 of 20 subjects examined for serum copper there were also found low values differing from the normal one.

Until quite recently the only disease entity in our speciality the development of which stood in association with iron deficiency was the Plummer Vison syndrome.

In 1960, Bernal drew attention to the significance of iron deficiency in the pathogenesis of osena. In his monograph, published in 1963 he presented convincing data, based on a large clinical and experimental material, in support of this opinion.

Histological pictures of mucous membrane of the upper respiratory tract in laboratory animals fed on a diet deprived of iron are very convincing. The metaplastic changes in epithellum, atrophy of mucous glands and changes in the connective tissue layer of mucosa resemble very much those in the histological picture of nose mucosa in patients with osena. His attempts at treating osena with iron proved encouraging.

We checked the results of Bernal's investigations and found them to be correct.

Then arose the question, if there are any other morbid conditions giving changes in the respiratory tract due to iron metabolism disturbances in the body and whether it is only the iron metabolism that is disturbed or perhaps there are also some other trace elements involved which are deficient or excessive in those morbid conditions. In the first stage of our investigations, aimed at answering the above questions, we studied a disease with a pathology of which is still obscure, although the entity was described nearly 100 years ago. It is scleroma, a disease of the upper respiratory tract, in which the specific granulation is undoubtedly due to the infection by a microorganism specific to this disease. A proof of this is the efficacy of treatment with appropriate antibiotics and the behaviour of

## DISCUSSION

*M Portmann* Vous obtenez une réponse pour l'eau froide et pas de réponse pour l'eau à température ordinaire. Pensez-vous que cela prouve qu'il y a beaucoup de fibres sensibles dans la corde du tympan? J'ai en effet travaillé les nerfs de l'oreille et la corde du tympan en utilisant des techniques histologiques et je n'ai trouvé que très peu de fibres de type sensitif beaucoup de fibres de type sensoriel et végétatif (il s'agissait de techniques nerveuses spéciales permettant des différences tinctoriales selon la nature des fibres)

*H House* The recent discussions at Oxford referred to by Mr Diamant indicated 30% to 40% of the cases for stapes surgery required sectioning of the chorda tympani to obtain adequate marking exposure. In our experience after 4 months 5% of the cases that have an undisturbed nerve at surgery have taste disturbance apparently due to fibrosis (revealed by section of the nerve on subsequent revisions) 7% have taste disturbance if the nerve is sectioned and 15% have taste disturbance if the nerve is stretched. From a subjective clinical viewpoint it seems better to section rather than to stretch the nerve. This same phenomenon is observed in regard to dryness of the mouth especially in post menopausal patients.

Would Mr Diamant please comment on this apparent compensatory phenomenon—what might be the compensatory pathway?

*F Escher* Can something be done after bilateral loss of the sense of taste caused by damage of the chorda?

*H Diamant* (Reply) to Mr Portmann Of course the chorda tympani contains sensory and/or sensitive fibres. Anyway they contain fibres sensitive to temperature and to touch. In fact, we use touch to test the experimental arrangement. In a nomogram of the chorda tympani made by Costen it seems clear that it must contain sensitive fibres.

to Mr House I am not sure that a compensation objectively ever happens when the chorda tympani is cut. What happens to chorda tympani after operation is that the taste seems disturbed forever. Not so subjectively. There is also a great difference between people according to the sense of taste. Some will never have any trouble and if they are psychophysically examined before operation one often finds a very weak reaction to different sapid solutions.

The reason why patients bilaterally operated complain of dry mouth is probably that the submandibular glands in such high degree provides for the moistness of the oral cavity. It has constant flow of saliva in contrast to the parotid glands which only secrete on stimulation.

to Mr Escher There is no possibility of restoring the function of the chorda tympani according to taste. It is too sensitive. We have for instance never succeeded in splitting the nerve to get recordings from finer strands of the nerve.

This opinion is corroborated by a higher incidence of scleromatous infection in women of the age at which the iron deficiency appears.

It is not excluded that the endemic occurrence of scleroma in some regions is connected with a poor iron content in the water of those regions and consequently in the food of the population living there. Investigations in this direction should be taken up.

A less distinct copper drop in the serum of patients (in 13 cases out of 20 examined) seems to speak for the smaller importance of the deficiency of this element in the pathogenesis of atrophic changes in the mucous membranes of the respiratory tract.

Similar disturbances of iron metabolism in *ozena* and scleroma may indicate some relationship of the two diseases, expressing itself also in the allied bacterial flora found in mucous membranes of the respiratory tract in both diseases and in very similar clinical pictures of *ozena* and atrophic forms of scleroma.

The future will show if the exact knowledge of the relation between the deficiency of some trace elements, especially iron and the changes in the mucosa of the respiratory tract will bring us nearer to an explanation of the etiopathology of the morbid conditions mentioned here and perhaps it will also contribute to a better knowledge of the development of some other diseases in our specialty.

## RESUME

Chez 31 malades scléromateux (26 guéris par des antibiotiques, 5 exigeant du traitement supplémentaire et 3 non traités) on a déterminé le ni eau du fer dans le sérum à jeun et 3 et 6 heures après l'administration par la bouche d 180 mg d valat de fer. Chez 20 malades d entre eux on a déterminé l contenu de cuivre dans le sérum. Chez 20 examinés on a constaté l contenu du fer considérablement baissé par rapport à la limite inférieure de la norme chez 13 d entre 20 examinés pour le contenu de cuivre dans le sérum on constaté aussi leurs minimales, différentes de la norme.

## ZUSAMMENFASSUNG

An 31 Sklerom-Patienten wurde der Fe-Spiegel im Serum bestimmt. Von diesen Patienten waren 26 nur durch Antibiotika geheilt worden, 5 erforderten weitere Behandlung und 3 waren bisher unbehandelt. Die Untersuchungen wurden an den Patienten im fastenden Zustand und 3 und 6 Stunden nach oraler Verabreichung von 180 mg Ferrivalat durchgeführt. An 20 der Patienten wurde der Cu-Spiegel im Serum bestimmt. Es ergab sich dabei, dass bei 20 der Patienten der Eisengehalt im Serum unterhalb der oberen Normgrenze lag und dass bei 13 von den 20 auf Kupfer untersuchten Patienten auch der Kupferspiegel im Serum zu niedrige Werte zeigte.



serum reactions in patients with scleroma, the latter being an expression of antigenicity of a microorganism from the *Klebsiella* group. The patients with scleroma in its typical forms are found as a rule, in certain definite areas of the world but the cases of its atypical abortive forms mostly undiagnosed are scattered all over the countries of both hemispheres.

The etiopathologic obscurity of scleroma consists in the fact that the very infective agent does not account for the development of the disease. There must coexist another exo- or endogenic factor. A contact of many years of a patient with a healthy individual may not bring about any infection of the latter but under other conditions, even a short standing contact may result in the infection of the healthy individual. A husband hardly ever becomes infected by his wife. Men on the whole suffer from the disease less frequently than women do. Daughters of mothers with scleroma often themselves fall ill with the disease.

Another puzzling moment in the pathogenesis of scleroma was the fact of a frequent association of hypochromic anemia which used to be accounted for as the result of a specific infection.

We pointed out that this explanation was wrong. At the meeting of our Collegium held in Edinburgh in 1963 I presented a paper in collaboration with Dr Durska Zakrzewska based on the largest material ever published in which the possibility of an entire cure in 10 per cent of scleroma cases was pointed out on the basis of all the hitherto known criteria of curability.

In a group of 26 cured patients we compared the hemoglobin values of the period before cure with those determined at different times after the cure was completed, i.e. after the eradication of the specific infection. No essential difference was stated between the values found before and after cure which contradicts the statement of an infective origin of anemia. It is to be stressed however that among the patients cured we did not find so very low hemoglobin levels, before starting the treatment, as other authors did in their scleroma patients.

On assuming that the endogenic factor facilitating the specific infection in some individuals is a deficiency of iron and perhaps also of some other trace elements in the body we took up their determinations in the sera of scleroma patients and of those already cured of the disease.

Out of 31 persons (including 12 males) only in two cases was the serum iron normal. In all the others the iron values were much below the bottom limit recognised as the norm for either sex.

In some cases of patients cured we observed iron values as low as 40  $\gamma$  or even 30  $\gamma$  in fasting patients and rather high ones at 3 and 6 hours after oral load with 180 mg of ferric sulphate. The high iron binding capacity of the serum of scleroma patients and the very low values of the coefficient calculated from iron content in the serum of fasting scleroma patients and its iron binding capacity allow us to draw a conclusion that this primary iron deficiency in the body which is demonstrable even after elimination of the infective agent is the very factor facilitating infection.

This opinion is corroborated by a higher incidence of scleromatous infection in women of the age at which the iron deficiency appears.

It is not excluded that the endemic occurrence of scleroma in some regions is connected with a poor iron content in the water of those regions and consequently in the food of the population living there. Investigations in this direction should be taken up.

A less distinct copper drop in the serum of patients (in 13 cases out of 20 examined) seems to speak for the smaller importance of the deficiency of this element in the pathogenesis of atrophic changes in the mucous membranes of the respiratory tract.

Similar disturbances of iron metabolism in oxen and scleroma may indicate some relationship of the two diseases, expressing itself also in the allied bacterial flora found on mucous membranes of the respiratory tract in both diseases and in very similar clinical pictures of oxen and atrophic forms of scleroma.

The future will show if the exact knowledge of the relation between the deficiency of some trace elements, especially iron and the changes in the mucosa of the respiratory tract will bring us nearer to an explanation of the etiopathology of the morbid conditions mentioned here and perhaps it will also contribute to a better knowledge of the development of some other diseases in our specialty.

## RESUME

Chez 31 malades scléromateux (26 guéri par des antibiotiques, 2 exige nts du traitement supplémentaire et 3 non traités) on a déterminé le niveau du fer dans le sérum à jeun et 3 à 6 heures après l'administration par la bouche de 180 mg d sulfate de fer. Chez 20 malades d autre eux on a déterminé le contenu du cuivre dans le sérum. Chez 29 vaminés on a constaté le contenu du fer considérablement abaissé par rapport à la limite inférieure de la norme chez 13 d entre 20 examinés pour le contenu du cuivre dans le sérum on a constaté des valeurs minimales, différentes de la norme.

## ZUSAMMENFASSUNG

Bei 31 Sklerom-Patienten wurde der Fe-Spiegel im Serum bestimmt. Von diesen Patienten waren 26 zuvor durch Antibiotika ausgeheilt worden, 2 erforderten eine weitere Behandlung und 3 waren bisher unbehandelt. Die Untersuchungen wurden an den Patienten im fastenden Zustand und 3 bis 6 Stunden nach oraler Verabreichung von 180 mg Ferri sulfat durchgeführt. An 20 der Patienten wurde auch der Cu-Spiegel im Serum bestimmt. Es ergab sich dabei, dass bei 29 der Patienten der Eisengehalt im Serum unterhalb der unteren Normgrenze lag und dass bei 13 von den 20 auf Kupfer untersuchten Patienten nach der Kupferspiegel im Serum zu niedrige Werte zeigten.

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## DISCUSSION

G Bustamante We have in Mexico one big zone of ozena and rhinoscleroma and have never found a close relation except the geographical distribution. Is it possible to confuse the atrophic state of rhinoscleroma with ozena? Maybe the lower intake of protein has some intervention on the process? The predominance of ozena and rhinoscleroma in people with Indian blood is for me apparent.

I Friedmann Mr Zakrzewski has very kindly examined the sera of several patients seen in London and suspected of scleroma. These were all negative. Does he rely on electron microscopy for diagnosis? Does he relate scleroma and malignant granuloma?

A Zakrzewski (Reply) I only indicated the relationship between ozena and scleroma because we had the opportunity to observe not only a number of cases of ozena among the cases of scleroma in the same families but also the effect of treatment by an iron given intravenously is similarly encouraging. As to electron microscopy for diagnosis I have no personal experience. In my opinion scleroma and malignant granuloma are quite different entities.

## POSSIBLE VASCULAR REGULATORY MECHANISMS IN THE MUCOUS MEMBRANE OF THE UPPER RESPIRATORY TRACT

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These regulations take place above all, in the vascular system and are caused by vegetative-nervous irritations. The principle of regulation in which the arteriovenous anastomoses, being controlled by the nervous system, are considered as effectors is explained. In this connection hypoxia of tissue together with the infiltration of lymphocytes and plasmacells, play an important part.

Basically the terminal section of the vessels supplying the mucous membrane of the upper respiratory tract may be divided into three parts. The first part comprises the larger afferent and efferent vessels, the second the vascular regulatory systems, i.e. the precapillary arterioles and the arteriovenous anastomoses with their blocking and reducing valves, and the third the network of capillaries.

The network of the capillaries maintains the metabolism—both maintenance and functional—of the cells and tissues. It supplies via the internal circulation both the interstitial tissues and the parenchymatous elements of the mucosa, as required. The control of the capillary activity in the case of constant blood flow through the larger arteries, is logically explained by the activity of the arteriovenous anastomoses. This paper will, therefore lay particular stress on the vascular shunts, their localization, morphology, functions, and influence upon capillary and internal circulation of interstitial fluid.

Although the occurrence of arteriovenous anastomoses in the mucous membrane of the upper airways appears to be a common phenomenon, we nevertheless did our own histological studies on them, with the object of detecting morphological elements of a regulatory system in the mucosa, which on the one hand would be connected with the nervous, and on the other with the vascular system. The existence of such a regulatory system seems very probable since an increase in glandular secretion in combination with a swelling of the cavernous tissue—and the inverse processes, a decrease in glandular secretion combined with a decongestion of the mucosa—are anything but purely accidental phenomena. Rather we should term them a defective functioning of the regulatory system normally operating according to plan under regular conditions.

Parts of the mucosa from the septum in the vicinity of the boundary between ciliated and squamous epithelium were obtained fresh and fixed

in zinc iodine-osmium according to Champy (1963) as well as in formol, dehydrated by means of terpineol and embedded in paraffin. Serial sections were stained partly with hematoxylin eosine, and partly according to Pasini (Romels) combined with nuclear staining according to Hansen (Romels). Graphic reconstructions of arteriovenous anastomoses were obtained from the serial sections.

The histological examination of the above mentioned areas of human mucous membranes yielded the following findings. There were no nervous receptor elements of a regulatory system such as organized terminal bodies or any other conspicuous nervous formations, in the areas investigated. On the other hand effector elements, amongst which we include the arteriovenous anastomoses were present in great numbers. The number of arteriovenous anastomoses found were related to the volume of the specimen examined. Independently of the size of the mucous membrane specimen the relative mean distance from one anastomosis to the next was calculated to be between 1.3 and 1.4 mm. In the regions of the nasal mucosa studied the incidence of anastomoses was dependent on only one factor: the size of the object studied.

Arteriovenous anastomoses are variously situated in the mucosa. They are however predominantly located at a depth of 1-3 mm, so that they may be said to be located immediately before the terminal portion of the vascular system.

The vascular shunts vary morphologically ranging from simple direct connections from an arterial branch—which is, of course equipped with some flow-controlling system—into a venous branch to the highly complex forms of Hoyer-Grosser (Clara) organs (Fig. 1) with gradual transitions between these extremes. In the last mentioned forms, just as in the neuro-nivo-arterial glomera in the skin, it is possible to show after zinc iodine-osmium fixation nervous fibres as well as fibrillar nervous reticulum within the connective-tissue sheath covering the anastomosis. However all these formations clearly correspond to the descriptions given elsewhere in the literature. There are numerous indications of the functional significance of the arteriovenous anastomoses in the nasal mucosa. We shall in the following briefly explain the influence of the arteriovenous anastomoses on the peripheral vessels. The interstitial lymph passages begin at the arterial branch of the capillary, i.e. where the capillary filtrate is produced and end in the venous branch of the capillary where at least the major part of the interstitial lymph returns into the bloodstream. The hydrodynamic pressure is of controlling importance for the production of capillary filtrate. Any change in tension will therefore result in a change in the amount produced and probably also in the composition of the capillary filtrate. It will also have an influence upon the nutrition as well as the functioning of the mucous membrane. The hydrodynamic pressure in the arterial branch may however be greatly affected by the activity of the vascular shunts. At a constant blood flow an opening of the connecting

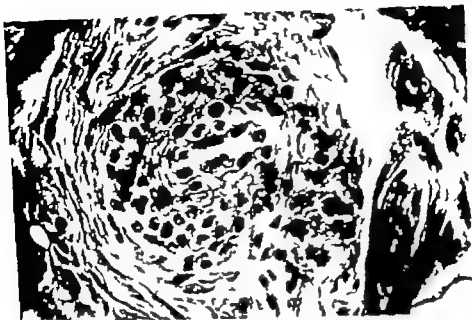


Fig. 1. Glomerula-like bodies of arteriovenous anastomosis in the mucous membrane of the nose.

branch of the anastomosis will result in a drop in the pressure in the capillary vessels situated peripherally from the anastomosis, whilst closure of the connecting branch will cause a pressure rise. Normally the connecting branches of the anastomoses will be constricted and dilated at intervals ranging between 2 and 30 seconds. Temporary complete contractions or dilatations may within certain limits still be considered to form part of the normal regulatory functions of an anastomosis. A permanent opening or closure of a vascular shunt, however will result in an equally permanent reduction or increase in the interstitial tension and, in consequence in a depression or overstimulation of tissue functions. In view of the profusion of vascular shunts in the nasal mucosa it seems more probable that drugs which influence the vasomotor functions act upon richly innervated arteriovenous anastomoses, rather than on the capillary vessels themselves. If one assumes that the therapeutic measures reach the arteriovenous anastomoses and consider in this connection also the factors of hydrostatic pressure capillary fluid exchange and the control of the internal circulation, this would explain the pathological changes found in vasomotor affections of the nasal mucosa much more plausibly and without fewer contradictions than do the traditional theories.

#### RÉSUMÉ

Ces régulations se déroulent avant tout dans le système vasculaire et sont déclenchées par des irritations neuro-végétatives. Le principe des régulations est

expliqué les anastomoses artéro-veineuses dirigées par le système neuro-végétatif étant considérées comme des facteurs effecteurs. Dans ce domaine, l'hypoxie tissulaire accompagnée d'infiltrations lymphoplasmo-cellulaires joue un rôle particulier

### ZUSAMMENFASSUNG

Diese Regulationen spielen sich vorwiegend im Gefäßsystem ab und werden durch vegetativ-nervöse Irritationen ausgelöst. Das Regulationsprinzip wird erklärt wobei als effektorische Anteile die nervös gesteuerten arteriovenösen Anastomosen angesehen werden. Dabei spielt die Gewebshypoxie gemeinsam mit den lymphozytär-plasmazellulären Infiltraten eine besondere Rolle.

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## STUDIES OF ETIOLOGY OF LARYNGEAL PAPILLOMA AND AN AUTOGENOUS LARYNGEAL PAPILLOMA VACCINE

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1 Electron microscope studies have failed to demonstrate virus particles in papillomas of four patients with laryngeal papilloma and one patient from whom the entire base of the papilloma was excised and excised from the tracheal wall.

2 No growth was obtained at the site of inoculation of the larynx of three female Rhesus monkeys whose true and false cords were inoculated unilaterally with 0.5 ml of a suspension made from papilloma removed from two children and one adult.

3 It was not possible to duplicate work reported previously which had indicated the presence of a species-specific virus capable of producing growth of tissue cultures with regrowth after blind serial tissue culture passages.

4 Blood samples were collected before and after vaccine therapy in patients with laryngeal papillomas so that in case a virus was isolated the viral agent could be used as the antigen in a serological reaction. Since the virus could not be isolated, there could be no serological evaluation of vaccine therapy.

5 The preparation and administration of an autogenous laryngeal papilloma vaccine is described with the results of this therapy as used in 11 patients.

6 Clinical evaluation showed that 28, or 85 per cent, were improved, 13, or 23 per cent, were considered unchanged and three or six per cent, deteriorated. Inadequate information was obtained in seven or 14 per cent.

7 The annual operation rate calculated for 37 patients who had adequate data before and after operation showed that the annual operation rate decreased in 29 patients (78 per cent), did not change in three patients (eight per cent) and increased slightly in five patients (13 per cent). The annual operation rate before vaccine therapy was 4.00; after therapy was 1.88, an average of 2.12 operations per year.

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An increasing amount of information concerning the etiology pathogenesis and clinical course of laryngeal papilloma is becoming available. Yet this serious entity, debilitating in many ways and occasionally terminating fatally, still presents intriguing aspects that often seem quite incongruous. Its species specificity and even its organ specificity have been established. The difference in the clinical appearance of the lesions in children and adults, in spite of having an identical histological picture is another of the incongruities. The influence of pregnancy stresses the hormonal component which has been a well established feature of the clinical course of the disease.

Factors inherent in the site of this variant of a common dermatologic condition have widespread influence on respiratory and communication function and ability. Not the least of these are the psychic trauma associated with a peculiar voice or a permanent or even temporary tracheostomy in a child or adult.

Experimental work relating to etiology and the multiplicity of therapeutic procedures that have been used in an attempt to effectively treat or influence the growths have been reviewed in a previous publication (Holinger *et al.*, 1962). A number of additional avenues of investigation have been explored which might have bearing on the basic nature of laryngeal papilloma. These are recorded in an effort to shed further light on problems of laryngeal papilloma. Some of the results are essentially negative yet they contribute incidental information. Others are of a more positive nature and will be given in more detail.

### *Electron microscopy*

The tissues from four patients who had laryngeal papillomas surgically removed were studied with the electron microscope. Ultra thin sections and negative staining were employed but no virus particles could be demonstrated. It was felt that since direct laryngoscopy and forceps removal of the papilloma was the choice method of surgery, a truly complete removal of tissue was not possible. In all probability the base of the tumor would need to be examined in order to demonstrate virus particles with the electron microscope. The only possible way to obtain a block of tissue in which the architecture of the papilloma and its centerlying structure were undisturbed would be to obtain a post mortem sample.

On November 15, 1963, a four year-old boy (M. B.) was admitted to Chicago's Children's Memorial Hospital because of extensive and rapidly recurring papillomatosis. A tracheostomy had been performed previously because of respiratory obstruction. At laryngoscopy and lower bronchoscopy it was found that the patient had papillomas above and below the tracheostomy tube, the growth extending to the carina. During the last of several endoscopic operations which had been only partially successful in clearing the trachea, a small hemostat was inserted into the tracheal open

ing and a large, intact papilloma with its stalk was "delivered" through the stoma and freed from the tracheal wall with a scalpel.

The removal of this complete papilloma directly from the trachea resulted in a specimen that was undisturbed and especially suitable for study with the electron microscope. The tissue was fixed, and when ultra-thin sections were examined, no viral particles could be demonstrated.

#### *Animal transmission studies*

On May 8, 1961 at The Children's Memorial Hospital, papilloma were removed from the larynges of two children. The tissue was triturated with a small amount of normal saline. In addition, the stored, frozen laryngeal papilloma of an adult male with recurring papillomatosis was triturated in an identical manner. Three mature female Rhesus monkeys were anesthetized with an intraperitoneal injection of Nembutal. When deep anesthesia was obtained, with the use of a laryngoscope the left true and false vocal cord of each monkey were inoculated with a total of 0.5 ml of a papilloma suspension. The right cords of the animals served as controls. The Brubaker-Holinger endoscopic color camera was used to record the procedure.

After one year the animals were sacrificed. There was no gross evidence of a papilloma at the site of inoculation. When the larynx was fixed and the site of inoculation examined microscopically, no abnormalities were observed.

#### *Tissue culture studies*

During the past five years, a sample of each laryngeal papilloma that was submitted for vaccine production was ground in mortar and an aliquot of the suspension was inoculated into tissue culture tubes. Three blind serial tissue culture passes were made for each papilloma suspension. It was not possible to demonstrate tissue culture cytopathology or evidence of viral proliferation. In these studies, it has not been possible to duplicate the work reported previously of producing growth of tissue cultures with regrowth on as many as eight passages (Holinger *et al.*, 1962).

#### *Serology*

Blood samples were collected from a number of patients before the start of autogenous papilloma vaccine therapy and then again after the administration of the vaccine was completed. It was postulated that if a virus could be isolated from the laryngeal papilloma, it would then be possible to use this viral agent as the antigen in a serological reaction. Since a virus could not be isolated, the serological evaluation of vaccine therapy could not be completed.

*Autogenous laryngeal papilloma vaccine*

A resumé of the effect of an autogenous vaccine used during the past five years in the treatment of papilloma of the larynx is presented in a current publication (Shipkowitz *et al.*, 1967). This is a continuation of the previous study and relates to further analyses of the clinical material. The effect of this therapy has been evaluated by the patient response to the vaccine and the comparison of the annual operation rates before and after the use of the vaccine in a series of 51 patients. Of the 51 patients, there were 31 males, 20 females; three were Negro, one Mongolian, and 47 Caucasian. Sixty-eight per cent were under 10 years of age, 31 per cent had required at least one tracheostomy, and in 16 per cent the papillomas had extended into the pharynx or the tracheobronchial tree. The duration of the condition prior to the start of vaccine therapy ranged from one to 391 months, with a median of 20 months. Histologic confirmation of the diagnosis was obtained in all cases.

The preparation and administration of the autogenous laryngeal papilloma vaccine has been as follows:

Fresh papilloma tissue was removed from the patient and placed immediately in sterile saline for storage at 4 C until the vaccine was prepared. Approximately 0.5 g of tissue was washed with sterile saline, minced fine with scissors and ground to a paste in a sterile mortar and pestle. The homogenate was suspended in 20 ml of sterile saline containing 1-1000 formalin. The resulting vaccine was incubated at 37 C for 24 hours and then tested for sterility by adding 0.5 ml of vaccine to two 10-ml tubes of thioglycollate broth and to one 10-ml tube of Sabouraud's broth. The broth tubes were incubated for 10 days: the Sabouraud's at 24 C, one thioglycollate tube at 37 C, and the second at 30 C. Sterile vaccine was then stored in a rubber stoppered vial at 4 C until used.

Each patient was inoculated intracutaneously with 0.25 ml of the vaccine thus prepared from his own papilloma and observed for any untoward reactions. If none occurred, the patient was injected with 0.5 ml of the vaccine subcutaneously. One week later the injection was repeated at a dosage of 1.0 ml. Vaccination was repeated each week thereafter at the 1.0 ml level until the vaccine was exhausted. When vaccine was administered to infants and small children the standard dosage was reduced by 50 per cent.

The amount of vaccine used on any one individual varied from six to 65 injections with a median of approximately 18 injections depending on response and availability of the vaccine. Adverse effects were reported in six of the patients (12 per cent): in two of these the reaction consisted of no more than local discomfort at the site of injection; a rash followed an injection in one; mild local induration with transient ankle edema was observed in one; and localized inflammation and moderate lymphadenopathy in a fifth. The sixth patient developed atelectasis of the right lower

and middle lobe bronchi after previously having papilloma of the pharynx, larynx and trachea. The extension of the process into the bronchus was considered reason to discontinue the vaccine therapy by the referring physician, although such extension was well within the usual clinical course of this condition.

# RESULTS

The results of therapy have been assessed by two methods (a) the clinical evaluation of the patients' overall response to the vaccine and (b) a comparison of the annual operation rates before and after initiating therapy. From a clinical evaluation of the 51 patients in this series, 28 or 55 per cent, were improved after vaccine therapy, 13 or 25 per cent, were considered unchanged and three, or six per cent, deteriorated during the course of the therapy or following it. Inadequate information for proper evaluation was obtained in seven or 14 per cent.

The change in the annual operation rate after a course of vaccine therapy could be calculated for only 37 of the 51 patients because, in some, complete data for calculating change in annual operation rate after receipt of vaccine therapy were not available. In others, vaccine was prepared from the papillomas removed at the first operation when the diagnosis was established which precluded comparative before-and-after calculations. Change in annual operation rate after vaccine therapy as calculated for the 37 patients for whom adequate data were available showed that the rate decreased in 20 patients (78 per cent) did not change in three patients (eight per cent) and increased slightly in five patients (13 per cent). Before start of vaccine therapy the mean annual operation rate for the 37 patients was 4.00; after receipt of vaccine therapy it dropped to 1.88, an average decrease of 2.12 operations per year. Statistical analysis showed that the probability of obtaining such a decrease by chance alone is less than one in 1000.

# RÉSUMÉ

L'étude préalable d'un vaccin autogène contre le papillome laryngé a été réalisée par l'analyse d'un plus grand nombre de malades observés pendant plus longtemps. Des résultats favorables ont été obtenus comme l'ont prouvé les réactions des malades et la fréquence annuelle des opérations avant et après le traitement par le vaccin. Les données cliniques de cette étude seront présentées et évaluées.

# ZUSAMMENFASSUNG

Ein früherer vorläufiger Bericht über ein autogenes Larynx-Papillom-Vakzin wird erweitert und schließt zusätzliche Patienten und eine längere Beobachtungszeit in günstige Resultate ein und werden durch eine

*Autogenous laryngeal papilloma vaccine*

A resumé of the effect of an autogenous vaccine used during the past five years in the treatment of papilloma of the larynx is presented in a current publication (Shipkowitz *et al* 1967). This is a continuation of the previous study and relates to further analyses of the clinical material. The effect of this therapy has been evaluated by the patient response to the vaccine and the comparison of the annual operation rates before and after the use of the vaccine in a series of 51 patients. Of the 51 patients, there were 31 males, 20 females, three were Negro, one Mongolian, and 47 Caucasian. Sixty-eight per cent were under 10 years of age, 31 per cent had required at least one tracheostomy and in 10 per cent the papillomas had extended into the pharynx or the tracheobronchial tree. The duration of the condition prior to the start of vaccine therapy ranged from one to 321 months, with a median of 20 months. Histologic confirmation of the diagnosis was obtained in all cases.

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Each patient was inoculated intracutaneously with 0.25 ml of the vaccine thus prepared from his own papilloma and observed for any untoward reactions. If none occurred the patient was injected with 0.5 ml of the vaccine subcutaneously. One week later the injection was repeated at a dosage of 1.0 ml. Vaccination was repeated each week thereafter at the 1.0 ml level until the vaccine was exhausted. When vaccine was administered to infants and small children the standard dosage was reduced by 50 per cent.

The amount of vaccine used on any one individual varied from six to 60 injections with a median of approximately 18 injections depending on response and availability of the vaccine. Adverse effects were reported in six of the patients (12 per cent). In two of these the reaction consisted of no more than local discomfort at the site of injection; a rash followed an injection in one; mild local induration with transient ankle edema was observed in one; and localized inflammation and moderate lymphadenopathy in a fifth. The sixth patient developed atelectasis of the right lower

fact that papilloma is a species-specific type of pathology. This is further apparent in experimental attempts to transfer papilloma between animal species, most of which are unsuccessful, with a few outstanding exceptions.

I appreciate Mr. Friedmann's confirmation that he too has been unable to identify virus particles in electron microscopy studies.

Mr. Angell James' work in ultrasound is most important, and his question in regard to the geographical distribution of papilloma is one of our on-going projects. Questionnaires have been sent to laryngologists in the Americas in an effort to help determine this distribution, but this work, as yet, has not been completed. We did find an unusual number reported from Haiti, which is similar to the findings of Mr. Angell James in regard to Thailand.

Mr. Ræed's question of duration of improvement is difficult to answer because all cases treated since 1960 are included in the study which was terminated about two years ago so that the results are those of a period of about five years.

Mr. Barrett's remarks of the effect of non-specific smallpox vaccine are of interest. It is our feeling that this is a species-specific problem in agreement with finding no effect on the growth by treatment of human papilloma with bovine papilloma vaccine.

Regarding Mr. Nishikawa's question of administration of vaccine in pregnancy we have not administered vaccine during pregnancy.

Bewertung sowohl der Reaktion des Patienten als auch im Vergleich zu der jährlichen Operationsfrequenz vor und nach Vakzinentherapie beurteilt. Klinische Statistiken über dieses Stadium werden gezeigt und bewertet.

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## DISCUSSION

*J. E. Bordley:* First I wish to congratulate the essayist on his presentation. The fact that Mr. Holinger was unable to reproduce the juvenile papilloma in the monkey vocal cord brings up the possibility that the tumor is specific for homio-sapiens.

It is of interest that a number of members of the pathology department at the Johns Hopkins Hospital some years ago obtained a sterile specimen of juvenile papilloma at the time of instrumental removal at laryngoscopy and immediately implanted it in a small incision in the skin on the upper portion of the forearm in an area free from hair.

The tissue lived and grew slowly for a number of years, at least six years, to my knowledge. It was still growing at the time the host moved to another university. Light microscope studies of the tissue after several years' growth showed it to be, in the pathologist's opinion, identical to a juvenile papilloma.

No attempt was made to carry out further transplants.

*I. Friedmann:* I beg to confirm that electromicroscopy of several cases failed to reveal a virus or virus-like particle. One case of the late Professor Ormerod has had at least 14 biopsies studied with entirely negative results.

*J. Angell James:* Has Mr. Holinger any information about the geographical distribution of papilloma? I was interested in the possible use of ultraviolet but found very few cases in the southwest of England. When visiting Thailand I was told that the disease is relatively common and 30 new cases are seen annually in Dr. Corns' clinic in the University Hospital in Bangkok.

*L. Rüdel:* How long do the improvements last after vaccine therapy?

*M. Barretto:* Barretto Predo, my former associate in São Paulo, has given a previous report on the effect of smallpox vaccination in cases of papilloma. The results are very similar to those of Mr. Holinger. I should like to ask him if he has done any experiment with other non-specific viral vaccines.

*W. P. Work:* Do you recommend the use of this antogenous vaccine during pregnancy?

*P. H. Holinger (Reply):* The contribution of Mr. Bordley confirms again the

fact that papilloma is a species-specific type of pathology. This is further apparent in experimental attempt to transfer papilloma between animal species, most of which are unsuccessful, with a few outstanding exceptions.

I appreciate Mr. Friedmann's confirmation that he too has been unable to identify virus particles in lectromicroscopy slides.

Mr. Angell James' work in ultrasound is most important, and his question in regard to the geographical distribution of papilloma is one of our on-going projects. Questionnaires have been sent to otolaryngologists in the Americas in an effort to help determine this distribution but this work as yet, has not been completed. We did find an unusual number reported from Haiti, which is similar to the findings of Mr. Angell James in regard to Thailand.

Mr. Rhedi's question of duration of improvement is difficult to answer because all cases treated since 1960 are included in the study which was terminated about two years ago, so that the results are those of a period of about five years.

Mr. Barrett's remarks of the effect of non-specific smallpox vaccine are of interest. It is our feeling that this is a species-specific problem, in agreement with finding no effect on the growth by treatment of human papilloma with bovine papilloma vaccine.

Regarding Mr. Risk's question of administration of vaccine in pregnancy we have not administered vaccine during pregnancy.



## COMPUTATION OF THE NYSTAGMOGRAM

N TOROK, MD and A J DERBYSHIRE, Ph.D

*From the Department of Otolaryngology University of Illinois Medical Center  
and the Illinois Eye and Ear Infirmary Chicago Ill U.S.A*

To study the interaction of the slow and fast component of the caloric nystagmus the total velocity of the slow components were plotted against time. The individual quick components were added similarly into a continuous curve. Whereas increased stimulations create increased slow phase velocity, the fast component speed remains constant. Graded caloric stimuli alter with similar proportions the slow component speed as well as the frequency count at the culmination. Incongruence of these two phenomena as well as traces on cathode ray oscilloscopes, indicates certain independence of the two phases of the vestibular nystagmus. Further evidence has been provided that both of these parameters, frequency count and slow phase velocity, are the best available expression of vestibular sensitivity.

Clinical neurootology is concerned with and predominately based upon the phenomenon of reactive or spontaneous vestibular nystagmus. The assessment of function and sensitivity of the vestibular apparatus is restricted mainly to the observation of this phenomenon. It became evident that prevention of fixation provides better observation. Alertness and elimination of undue light, sound or other distractions also were essential for reliable evaluation. Finally nystagmography fulfilled various desirable objectives for assessing these eye-movements. The photoelectric technique, in particular, may amplify the nystagmus to any desired magnitude. The records are available for detailed and specific studies and so without exaggeration the recording of nystagmus has reached a close to perfect level. These improvements enabled the evaluation of several parameters of the response. The velocity of the slow phase was found to be a characteristic feature; the frequency count per time unit proved to express specifically the sensitivity of function. These were great improvements over the past and gave greater security to the neurootologist at the time of these discoveries.

Standard stimulation and recording of the provoked vestibulocolic reflexes in healthy individuals provided the information necessary for establishing what may be considered as normal. Thus a reference became

This study was supported in part by U.S.P.H.S. NIH Research Grant NB-1711

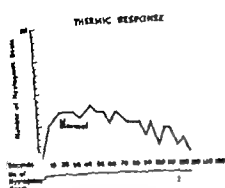


FIG. 1

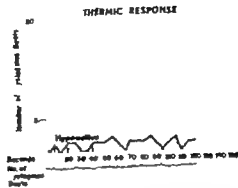


FIG. 2

FIG. 1 Normal postcaloric vestibulogram. The frequency of the postcaloric nystagmus is plotted on a coordinate system. The baseline marked 10 sec time units serves the time scale for the duration of the vestibular response. The ordinate represents the nystagmus frequency. The 10 of digits below the vestibulogram indicates the number of nystagmus beats in every 5 sec. The culmination is 17 beats for 1 consecutive 5 sec time unit which makes 15 for the 10 sec time peak of the response.

FIG. 2 Hypoactive postcaloric vestibulogram. The duration of this response does not differ from that of the normal caloric reaction. There is marked reduction in the nystagmus frequency. The intensity is flat curve. The maximum frequency or culmination for 10 sec is 2. A acoustic tumor was diagnosed and successfully operated on.

available to discriminate between physiological and pathological, i.e., normal and diseased.

Since it is easy to differentiate individuals with normal hearing from those with defective hearing on the basis of the pure tone audiogram it was logically expected to identify the normal and abnormal vestibular reflex responses.

By plotting the frequency of the postcaloric nystagmus on a coordinate system, the average normal (Fig. 1) can be readily distinguished from the pathological, which may be either below (i.e. hypoactive) or above (hyperactive) the limit of responses obtained in normal subjects.

The decreased response is variably termed as hypoactive reaction, decreased sensitivity vestibular paresis, etc (Fig. 2). Such a finding is accepted objective evidence of a lesion. The localization or site of the pathology is not immediately defined. Other clinical data and an integration of such findings with all the available vestibular and cochlear responses should facilitate the final diagnosis.

The increased response (Fig. 3). The term hypersensitivity is incorrectly applied to these responses. There is no increase in sensitivity above the normal level in sensory organ physiology. Instead the provoked nystagmus as a reflex response is exaggerated. This neuropathological phenomenon is similar to the increased tendon reflex indicating a lesion of the pyramidal

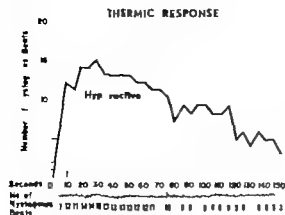


Fig 3

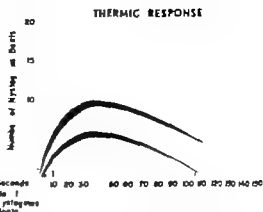


Fig 4

**Fig. 3** Hyperactive postcaloric nystagmogram. The nystagmus frequency is increased considerably right at the onset. The culmination reaches 14 and 15 beats in the peak two consecutive 5 sec period. So the culmination is 29 far above the average normal. This increased vestibular response indicates a central lesion. A meningioma in the middle cranial fossa was diagnosed.

**Fig. 4** The normal range of the nystagmus frequency and particularly the culmination within the normal range is indicated by the shading. Identification of the abnormal becomes evident when it is below the shaded area.

system produced by some defective inhibitory mechanism. Such a nystagmus finding may not be a vestibular abnormality per se, but rather a lesion of the inhibitory mechanism in the nystagmus pathways. It can be postulated with certainty that an increased nystagmic response is a sign of central nervous system pathology. More specific meaning arises when such a finding is unilateral.

The study of the frequency of the provoked thermic or rotatory nystagmus thus facilitates a fairly clear discrimination between normal and abnormal (Fig 4). For any practical purpose the clinician can depend upon the culmination value and frequency behavior of the nystagmus sequence.

We have advanced considerably in vestibular function evaluation since the time when the nystagmus duration was checked with a stop watch. With all the improvements and refinements in technique and evaluation principles, it would be an overstatement to say however that we have arrived at a fully satisfactory answer. Most confusing may be the wide variations of responses in normals. Overlapping responses between findings considered as normal and abnormal creates uncertainties. The search for more clues in the nystagmus record must therefore be pursued.

In our present study instead of concentration upon nystagmic details the interaction of the slow and rapid components were analyzed. The intriguing composition of the two components created problems and controversies for almost a century. The prevalence of the slow phase as the primary vestibular reflex is generally accepted. The role and significance of

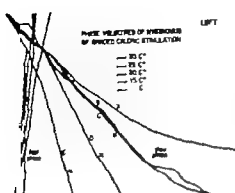


FIG. 5.

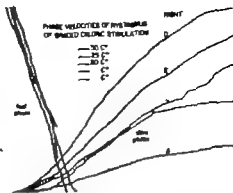


FIG. 6.

FIG. 5. Graded stimulation response of the left horizontal canal. The slow and fast component speed of the tonic nystagmus are summed. The five curves of the slow phase mostly represents the effects of the five graded stimulation. (A: 30°C, B: 25°C, C: 20°C, D: 15°C, E: 10°C of 100 cc of water). While the low component speed gradually increases with the stronger stimulation, the fast component speed remains unchanged. The number on each slow phase curve is the respective maximum frequency per 10 sec (culmination lines).

FIG. 6. Graded stimulation response for the right horizontal canal.

the rapid component, however, is not settled satisfactorily. It is assumed to be a compensatory phenomenon. The anatomical origin and neural pathways controlling the fast phase are not fully understood.

In our investigations, the following procedure was carried out: rotatory and thermal nystagmograms were obtained from normal healthy individuals by using the photoelectric (PENK) principles. A series of graded stimulations were applied. Although both rotatory and caloric stimulations were performed, this report will describe only the caloric responses. Each subject received five pairs of caloric stimulations. For the first pair of tests 30°C water was used (100 cc in 20 seconds with the head in the optimal position, i.e., 60° back from the upright). The consecutive stimulation contained 25, 20, 15, and 10°C water. A minimum of five minutes waiting period between the two stimulations was maintained; care was taken that all the testing procedures were executed in a standard manner.

The nystagmograms were analyzed by summing all slow components along each individual response, keeping their relative time relationships (Fig. 5). The slope of this curve at any point expresses the velocity of the low phase at that moment. The individual fast component velocities were also summed. This comparison of all slow phases against all rapid components creates one giant nystagmus with the speed, time, and direction of motion represented (Fig. 6).

On one chart the response to all five graded stimuli are plotted. The five nystagmus patterns clearly show the nature of this vestibular reflex. To

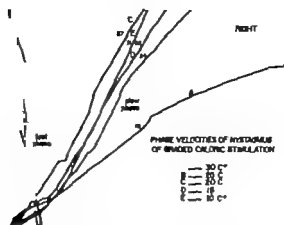


FIG. 7 Irregular slow phase velocity response to graded stimulation. The velocity following 20 C stimulus is faster than the slow phase speed of 15 C and 10 C stimulations. The culmination values are proportional.

present all the characteristics of the response the maximum frequency at the peak of the reaction i.e. the nystagmus culmination was also counted.

As expected, the increased stimulation strength resulted in an increasing response of slow phase velocity and maximum frequency count. The most striking fact is that while the slow phase velocity is increased with more or less regularity and proportion the velocity of the rapid phase remains conspicuously identical regardless of stimulus strength. On the other hand the maximum frequency count of the fast phase changes proportionately with the degree/sec of the slow phase curve.

The range of increased response most frequently was gradual but the magnitude of the increase could differ (Fig 7). The slow phase velocity ranged between 12 /sec for 30 C water to 32 /sec for 10 C water whereas another subject exhibited a 30 /sec through 39 41 66 to 80 /sec gradation for the same stimulation series. The frequency culmination similarly (Fig 8) varies between 10 beats per 10 sec in the first mentioned case for 30 C water and 23 beats at culmination for 10 C stimulation. In the second mentioned subject the frequency increased gradually for 13 beats to 18 21 32, and to 41 beats for 10 C temperature water.

The mathematical relation between stimulus strength and response can approximate linearity. The majority of our subjects did follow such a rule. Anomalous findings did occur in some instances, however when one stimulus response out of the five was disproportional to the rest (Fig 9).

There is no clear explanation to the anomalies. They do occasionally occur and it is familiar for all those involved in regular vestibular testing. A number of factors have been mentioned as reasons for such discordance. Mental distraction either by undue nonspecific stimulation or diminution of activity such as drowsiness or mental excitement are considered as common causes. This discrepancy occurred in the measurement of slow phase velocity just as well as in frequency culmination. It is noteworthy that an

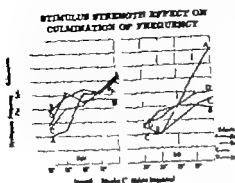


FIG. 8.

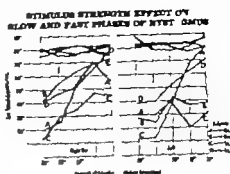


FIG. 9.

FIG. 8. The culmination frequency shows proximal linearity with the stimulus strength. The range of increase is mostly gradual, but the magnitude of increase differs (compare B and A curves on the left side)

FIG. 9. The slow phase velocity increases according to the stimulus strength. The scales of speed spread over a wider scale than those of the frequency culmination

Incongruity of one single response never affected the slow phase velocity and frequency maximum at the same time. This observation was unexpected and contradicts a direct interrelation of the two phenomena.

Our findings support and confirm our previous assumption and clinical experience that the frequency of the evoked nystagmus is an adequate measure of intensity of the reflex.

By studying the slow and fast component interchange, it was possible to photograph a series of consecutive nystagmus beats on the oscilloscope with superimposing eight nystagmus on the screen (Fig. 10). In spite of the identical slow component speeds, the fast phase appeared at different time intervals. Furthermore, by studying individual fast phase appearances, (Fig. 11) it is sometimes evident that the slow phase has no constant velocity and the fast phase may occur not at the height of the slow phase speed, but after some decrease of the slow phase velocity.

It becomes questionable therefore whether the frequency depends upon the slow component speed. The slow phase velocity is a direct vestibular reflex; however it is possible that the fast component may also be a direct vestibular response. The slow phase velocity and the frequency of the fast phase are hanging congruently and proportionally to the stimulus strength. This relation was studied statistically with the culmination count as the dependent variable and the maximum slope of the slow phase velocity as the independent variable. The slope of the regression was 0.32, indicating a proportionally greater sensitivity of the culmination count, than of the slow phase velocity. The correlation (Pearson  $r$ ) equals 0.83 with a correlation coefficient of 0.69. This is evidence of a strong relationship, so that 60% of the variation of the culmination count can be predicted from the

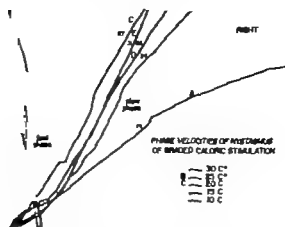


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Wechselwirkung dieser beiden Vorgänge zu gewinn n. Die Ergebnisse der Analysen und die Hypothesen die ihnen unterliegen sowohl als die sich daraus ergebenden weiteren Folgerungen werden besprochen.

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## DISCUSSION

*M. Arslan:* The problem exposed by Mr. Torok, that is the observed (with computer work) correlations between the slow and quick phase of nystagmus, can find a physiological explanation in the dependence existing between "intensity" of the afferent vestibular excitation and the "intensity" of the response of the reticula and secondary vestibular pathways, which elaborate the quick phase of nystagmus.

*H. Dasi:* By the term "culmination of frequency" do you mean the peak frequency of slowing the stimulation?

A model for the relation between the slow and fast components is suggested by the discharge of impulses in auditory nerve fibers. The fast component may be triggered by the slow component after an interval that is directly related to the slope of the slow component on which is superimposed a random process. I hope this model will prove useful.

*C. R. Pfall:* I should like to confirm M. Torok's opinion that the maximum response following thermic stimulation of the labyrinth—i.e. the culmination period of nystagmus—is a rather important parameter with respect to the evaluation of thermic nystagmus. Dr. Torok has shown a particular type of culmination which he calls hyperactive type. According to our own observations, this pathological increase of nystagmus intensity is always a symptom of central vestibular lesion. We found it more frequently in cortical or subcortical lesions of the central nervous system than in lower brain stem lesions and hence assumed this particular pattern of the caloric response to be a symptom of supratentorial vestibular lesion. I should like to ask Mr. Torok if he may confirm our previous observations by his own findings.

*G. Nohlsman:* The correlation between the speed of the slow phase and the triggering of the fast phase is in my opinion exposed to too many variables that it is difficult for me to see clearly correlating. As an example I would like to mention an experiment I recently had the opportunity to learn about in Dr. Henrikson's laboratory in Lund. It was able to show that nicotine from amok





FIG 10

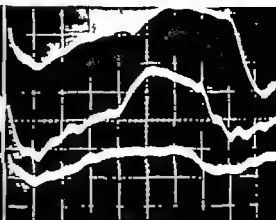


FIG 11

FIG. 10 Superimposition of 8 nystagmic beats (triggered by voltage of fast phase 1 cm=0.1 sec, amplitude gain constant) Note the loops of slow phases are superimposed and consistent while the fast phase subsequent to the triggering is scattered.

FIG. 11 Three individual sweeps, each triggered by a fast phase (1 cm=0.1 sec and amplitude gain constant) Note that subsequent fast phase appears after maximum of slow phase is reached (even at a decrease from maximum in one sweep)

slope of the slow phase velocity. There is less than one possibility in 100 000 that such a relationship could be found as a result of chance.

These observations and principles form an adequate basis on which we are developing a program for electronic computation of the nystagmogram. Our nystagmic data are recorded in the conventional manner but transferred simultaneously on an FM magnetic tape which provides the information to the computer. Immediate calculation of the slow phase velocity integrated with a continuous frequency count is expected to provide further specified and prompt answers to measure and assess vestibular sensitivity.

#### ACKNOWLEDGMENT

The authors wish to express appreciation to Miss Linda Poznanski B.A. for her valuable assistance in testing, reading the nystagmograms and charting the records.

#### RÉSUMÉ

Le paradigme que nous utilisons pour analyser le nystagmogramme essaye non seulement de mesurer chacun des deux constituants individuels du nystagmus mais aussi d'exprimer leur interaction. Les résultats de ces analyses, les hypothèses et les implications qui en découlent seront discutés.

#### ZUSAMMENFASSUNG

In unserer Analyse des Nystagmogramms versuchen wir nicht nur die Werte beider Nystagmuskomponenten zu bestimmen sondern auch eine Einsicht in die

## AVERAGED-EVOKED-RESPONSE EEG AUDIOMETRY IN NORTH AMERICA

H. DAVIS, M.D.

*From the Central Institute for the Deaf, St. Louis, Mo., U.S.A.*

Averaged evoked responses recorded from the vertex (V potentials) are a useful basis for "physiological audiometry" in infants and young children. Their responses are slower and more variable than in older children and adults. A response to tactile stimulation is a useful guide to the form of the auditory pattern if the auditory threshold is high. Good agreement among the eight or ten most active laboratories in North America has been reached on the desirable parameters of stimulation and recording. The values are summarized and references are given to significant recent publications from each laboratory.

In 1964 in Würzburg we described the slow cortical responses, which we now call the vertex or "V" potentials, that are evoked by auditory, tactile and visual stimuli, and we reported our first experiences in their use as an endpoint for what I now like to call "physiological audiometry" (Davis, 1965). Since that time both we at Central Institute for the Deaf and our colleagues in other laboratories in the USA and Canada have continued to study them. One approach relates them to the maturation of the nervous system in infancy (Engel, 1967; Ellingson, 1964). Another approach relates them to the depth of sleep (Williams *et al.* 1964; Goff *et al.* 1966). Another is concerned with modifications related to neurological abnormalities (Rapin *et al.* 1966; Barnett & Lodge, 1966). Others study their physiology (Cody & Bickford, 1965; Davis, 1966; Rapin *et al.* 1966) and still others (who are not included in our list of references) their relation to the intellect of the subject, his expectations and the amount of information he receives. On the whole the photoic responses are more popular than auditory, largely because the early response of the primary projection area of the visual cortex can be recorded and studied.

Most of those interested in the audiometric use of V potentials have studied sleeping infants or young children, using a sedative such as chloral hydrate when necessary (Appleby, 1963; McCandless & Best, 1966; Price *et al.* 1966). The Central Institute for the Deaf, however, is not a medical institution. We therefore never use a drug but have tried to adapt our tech-

This investigation was supported by Public Health Service Research Grant N B-3834 from the National Institute of Neurological Diseases and Blindness.

ing dramatically changed the correlation between slow and rapid phase. The speed of the slow phase remained unchanged whereas the rapid phase became more pregnant and the speed of the rapid phase was decreased. Presumably this refers to the influence of nicotine on the reticular system as one of the sources of influences on the correlation between the two phases.

*L. B. W. Jongkees* As regards the stimulation used in these experiments I want to point to the fact that the caloric stimuli is very impure and cannot very well be used for quantitatively experiments. I hope that Mr. Torok and Mr. Derbyshire will repeat their experiments with a purer form of stimulation like e.g. rotatory acceleration. It is very good that the authors brought forward again the extreme importance of the wide variations of the vestibular reactions in normals.

*N. Torok (Reply)*

to Mr. *Arslan* Essentially offered further explanations to our assumption. It is possible indeed that contrary to our long established concept the fast nystagmus component is more dependent upon direct vestibular effect than on the velocity of the slow phase.

to Mr. *Davis* The term "culmination" is a commonly used expression in vestibular terminology. It refers to the maximum or peak intensity of the post caloric nystagmus. The suggestion of a model to be constructed in order to better explain the slow and fast phase relationship was already conceived by us. Dr. Davis' advice will certainly encourage us in our further efforts to clarify the origin of the fast component.

to Mr. *Pfall* The hyperactive vestibular responses must be considered pathological and of central origin. The mechanism causing this phenomenon might be explained by an example from neuropathology. Increased tendon reflex indicates some pyramidal lesion where the inhibitory mechanism in the reflex arch is damaged. The increased nystagmic response can be caused by a lesion to the inhibitory mechanism within the nystagmus pathways. Such a lesion might not be a direct vestibular defect and can be located within the eye muscle coordination system. The vestibular stimulation then evokes an uninhibited oculomotor system resulting in an increased nystagmic response.

to Mr. *Dohlman* The experiment mentioned by Mr. Dohlman serves as support to our contention. Cigarette smoking irritates perhaps the central vestibular apparatus in a special form where the slow phase remains unaffected but the central source or origin of the fast component responses with an increased reaction.

to Mr. *Jongkees* who terms the caloric test "dangerous". It was mentioned earlier that in our study graded rotatory stimulation had been executed along with graded caloric testing. Because of time limitations our present report was restricted to the caloric responses. However until some better or improved testing or stimulating method becomes available we must depend upon the caloric stimulation.

The use of "thermic" instead of "caloric" testing may be justified. Barany invented the word "caloric" more than 60 years ago. What he really meant to define was the effect of heat upon the endolymphatic fluids. Caloric is not involved in the reaction. On the other hand in our weight conscious society the term "caloric" has a specific meaning, certainly not applicable to the testing procedure of the vestibular receptors. "Thermic" is not a new term in this respect, but certainly a more appropriate expression than "caloric".

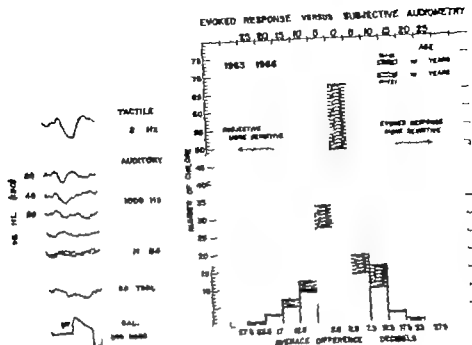


Fig. 1

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FIG. 1 Auditory and tactile responses of normal adult, showing the similarity of tactile and auditory responses and the presence of a dietary response at 8 dB hearing level (ISO) (From De L & Klenzweiler *J Speech Hearing Disorders*, 1973, by permission.)

Fig. 2. Distribution of the differences between estimates of the physiological evoked-response thresholds and isolated finger-response threshold for 162 children with impaired hearing: 1 Control; 2 test for the Deaf. Each rect. cell represents the a stage of the differences: 1 500, 1000 and 2000 Hz. The greenest 1 good for 4-6 years (crosses) as for 7-15 years of age (hatched). (From Davis, Hirsch, Shalwitz & Bowers, *J. Speech Hearing Research*, 1966, by permission.)

larger number of responses, but then the danger of a change of state in crosses.

The patterns of response of a given child are not completely variable, however. If they were we could not extract an "average" response from the background. There is still an individuality of pattern but it is not as clearly defined and reproducible as in an adult. On the other hand the differences across children may be so great that the waves seem to be in almost exactly opposite phase positive versus negative. This makes it quite impractical to simply rigid rules, such as we would like to write in order to program a computer to recognize the positive patterns.

A very useful procedure for identifying a small response which only appears at stimulus levels near the upper limit of the audiometer is to record a response to tactile stimulation, and to superimpose this pattern

nique to the requirements of the restless and sometimes antagonistic young children most of them two to six years old who come to our hearing clinic for evaluation. We have simplified and standardized both our procedure and our equipment and we hope that a commercial model built to our specifications by the Princeton Applied Research Corporation will be on the market at a reasonable price by the summer of 1968. We have been encouraged to proceed in this development by the excellent agreement among a number of the investigators named above who assembled in Los Angeles at the invitation of Drs. Victor Goodhill and Edgar L. Lowell. All agreed that the method held great promise for audiometric assessment of children suspected of auditory impairment in the difficult but important first three years of life. The following details drawn from our own experience express, we believe, the consensus of that group.

First we can estimate with good accuracy the behavioral (or finger response) threshold of hearing in children of four years and older from their V potentials. The V potential is an on-effect and its amplitude is not closely related to the loudness of the stimulus so that there is no necessity that the two thresholds, physiological and behavioral, should coincide. Fortunately the agreement is quite good, particularly when, as in our case, the observers who estimate threshold from a set of V potential records by interpolation or by extrapolation, have the benefit of constant and immediate feedback from comparison of their estimates with subsequent behavioral tests. Fig. 1 illustrates a series of (adult) auditory V potentials recorded with our simplified clinical evoked response audiometer. We shall comment in a moment on the great value of a tactile response as a guide in cases where the auditory response is weak or absent. Fig. 2 shows the summary of our comparison of evoked response audiometry with classical behavioral "finger response" audiometry for all of the children at CID who had both measurable hearing and identifiable V potentials at frequencies 500, 1000 and 2000 Hz. For the first two years we employed tone pips (filtered clicks) as stimuli, in the third year we substituted standard audiometric tone-bursts. The agreement between the two methods was equally good. The figure shows that age, at least for 4 years and older, is not a significant factor. Our estimates are neither better nor worse for those 4 to 6 years old than for those 7 through 16 years old.

We have already reported (Davis, 1966) that the V potentials of children are more variable than those of adults. The variability is particularly troublesome for very young children. It is not only that a young child, particularly an infant, may suddenly fall asleep during a test or pass from light sleep to deep sleep. The monitor EEG can at least give warning of such changes. Even with a constant background EEG pattern the latency as well as the amplitudes of particular waves may vary considerably from one trial to another. The physiological "noise" of the background EEG, which is often semi-rhythmic and of high voltage, contributes an important part of this variability. In principle it could be reduced by averaging a

Repetition rate, for waking subjects, 1 per sec. sleeping, 1 every 2 sec. (This repetition rate gives the maximum voltage per minute but it is not critical)

Number summed in a trial 30 to 64 Some workers prefer summing fewer responses at a slower rate

Duration of sample following each stimulus 500 msec (waking) or 1000 msec (sleeping)

Time constant of the EEG machine long enough to record 3-per-second delta waves without gross distortion or phase shift

With a skillful and experienced assistant to apply the electrodes and to amuse the child with toys, pictures, puppets, etc., we can usually obtain 20 or possibly 24 one minute stimulation periods, with one or two play periods interpolated, before the child becomes too restless. The total time is a little over an hour. With a reasonably cooperative child and using on-line strategy like the game of "20 questions" we often obtain a five frequency audiogram for each ear in this time.

### RESUME

Les réponses évoquées moyennes auditives recueillies sur le vert x (potentiels V) sont une base valable pour un audiométrie physiologique chez le nourrisson et chez le jeune enfant. Ici les réponses sont plus lentes et plus variables que celles du grand enfant et de l'adulte. Une réponse à une stimulation tactile sert de référence pour déterminer la forme du pattern, lorsque le seuil auditif est levé. Entre les huit ou dix plus importants laboratoires nord-américains, un excellent accord est intervenu pour fixer les meilleurs paramètres de stimulation et d'enregistrement dont les valeurs sont données. Pour chaque laboratoire la plus récente et significative publication est rapportée.

### ZUSAMMENFASSUNG

Elektronisch ermittelt am Schell I abgeleitete evoked responses (V Potentiale) stellen eine wohl begründete Basis für eine physiologische Audiometrie von Säuglingen und Kleinkindern dar. Die Reizantworten sind langsamer und variabler als bei älteren Kindern und Erwachsenen. Die Antwort auf taktile Reize wird als wichtiger Anhaltspunkt für die Beurteilung von Hörstörungen bei erhöhter Hürschwelle unter 20 oder 30 Minuten. Zehn Laboratorien in Nordamerika konnten eine gute Übereinstimmung über die wünschenswerten Stimulations- und Registrierparameter erzielen. Diese Werte werden zusammengefasst, und es wird auf je eine neue bedeutende Publikation der einzelnen Laboratorien hingewiesen.

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The following references are included in recent studies in USA and Canada of the low frequency potentials in the evoked response audiometry

## VERTEX POTENTIALS IN CHILDREN

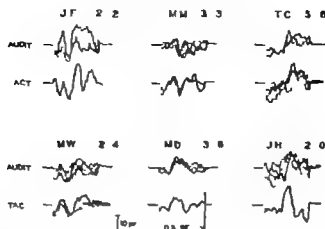


FIG. 3 Auditory and tactile V potentials of six young hard-of-hearing children. The auditory responses were evoked by loud tone bursts of different frequencies. Note the general similarity between auditory and auditory and between auditory and tactile for the same child, and the considerable differences across children. The latencies-to-peak in M.D. (age 3 years 8 mo) are very unusual although not unique.

on the unknown pattern on a trans-illuminated surface. The eye detects similarities of pattern very readily in this way even in the presence of considerable noise. Of course if a large clear auditory response appears at a high stimulus level it can be used instead of a tactile response to identify small V potentials near threshold. It should be remembered, however, that the latency of a tactile response is some 20 to 30 msec longer than the auditory response and that very near threshold the latency following a tone burst may be significantly lengthened (Rapin *et al* 1966). Tactile responses can usually be recorded from young sleeping children without awakening them.

Fig. 3 illustrates the variability of V potential patterns among children and the similarity for each child between his auditory and his tactile responses. In several cases we have superimposed two or three average responses to indicate the variability due largely to "noise" from one trial to another.

The parameters of stimulation which were agreed upon as desirable for routine clinical evoked response audiometry and which we have incorporated in our design are as follows.

**Auditory stimulus** tone bursts from a standard audiometer calibrated to ISO scale with rise time between 20 and 30 msec. (Alternative transducers for infants are Sharpe earphones in circumaural cushions and a loudspeaker.)

**Tactile stimulus** a vibrator like an oversized boneconduction vibrator applied to the palmar surface of the fingers. The hand lies, palm up on a pad of sponge rubber. 120 Hz tone bursts from the bone-conduction output of the audiometer suitably amplified are appropriate.

*H Davis (Reply)* The variability of the patterns follows two definable trends. The patterns are slower the younger the child and they are slower in sleep. The greatest difficulty arises when the background EEG is of high voltage and that of the potential is small. These are individual characteristics and there is no necessary relation between the two. We repeated the tests on the children with whom we made the worst errors and we tended to make the same errors on the second test. The problem is to recover a small signal in a high level of background noise within a reasonable time. We make a compromise here.

We are investigating the possibility that certain variations in particular waves may reflect neurological abnormalities, but as yet we have no definite results to report.



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The Central Institute for the Deaf  
St Louis, Mo. U.S.A.

## DISCUSSION

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## ON ACOUSTIC RESEARCH AND ITS CLINICAL APPLICATION

J J ZWISLOCKI Sc.D

Syracuse NY, U.S.A

Recent acoustic research employing improved instrumentation and rigorous analysis has led to a rather detailed understanding of the normal and pathological middle-ear function, and to a new diagnostic methodology. This methodology complements the audiometry.

### INTRODUCTION

I was asked to review for you some of the recent acoustic research that has been going on in my laboratory at Syracuse University and to discuss some of its clinical applications. Before I do so let me digress a little and point out to you a paradox in the examination of the ear that seems to have escaped notice. The paradox concerns testing of the middle ear function.

The middle ear transmits sound by means of minute, submicroscopic vibrations. These vibrations are the essence of its functioning and it is adapted to them. It is not designed for large visible motions which are known to distort its normal mode of operation. Neither is it designed to transmit light, as all those who have tried to see beyond the eardrum must know. Yet, practically through the whole history of otology and audiology men have made strenuous efforts to avoid sound and small vibrations in the examination of the middle ear and to use light and large visible displacements. Audiometry which uses sound provides only an indirect test of sound transmission and cannot be regarded as a direct examination of the middle ear.

The limitations of visual inspection and of hearing tests often leave the middle ear shrouded in a veil of diagnostic mystery.

### METHOD

We have attempted to fill the obvious gap in the methodology of ear examination by developing what we call an acoustic method. The method takes as a point of departure the pioneering work of Dr. Metz performed in the 1940's, and culminates in a clinical instrument and a table of acoustic symptomatology. It is designed to complement the otoscopic examination and the hearing tests. It provides a check on the often uncertain results of bone conduction testing and permits a diagnostic differentiation among

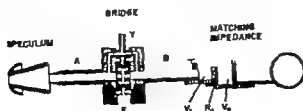


FIG. 1 Longitudinal section through the acoustic bridge drawn schematically (From the *Journal of Speech and Hearing Research*.)

middle ear malfunctions. In addition, it allows otherwise unnoticeable small changes to be detected.

The method is based on a partial reflection of acoustic waves at the eardrum. This reflection depends not only on the state of the eardrum but also on that of the ossicular chain and the cochlear windows. Even the cochlea has an effect on it. Through acoustic measurements on normal and pathological ears and with the help of anatomy and acoustic theory we have been able to analyze the middle ear function in detail and to correlate the acoustic changes measured at the eardrum to middle ear pathologies. In a way we have learned to look acoustically beyond the eardrum.

The reflection of sound waves at the eardrum depends on the effective resistance, stiffness and mass of the middle and inner ear system. It should be noted that, in the technical language, resistance means only one force component specifically the one that results from friction. The latter arises in ligaments, muscles, and ossicular joints of the middle ear. However, the main acoustic resistance component of the ear stems from the wave motion in the cochlea, as has been demonstrated first theoretically and later experimentally. It also should be mentioned that, in mechanical systems, the mass interacts with stiffness in a way that tends to reduce the effect of the latter and make the system appear more compliant. The effect is most pronounced at the resonance frequency where the system becomes infinitely compliant. In the normal ear the main resonance occurs somewhat above 1000 Hz.

The instrument we have developed for the acoustic examination of the ear is based on Schuster's principle of an acoustic bridge. We have succeeded in designing it in such a way that it measures directly the effective acoustic resistance and compliance at the eardrum. The first slide (Fig. 1) shows its schematic drawing.

At the far left is a special speculum with a soft plastic flange. It is designed to properly place and seal the bridge in the ear canal. The bridge itself contains two main tubes, A and B, which are symmetrical with respect to a central electroacoustic transducer E. The transducer radiates sound waves into tubes A and B in phase opposition. The wave in tube A is partially reflected at the end of the tube and partially at the eardrum. The wave in tube B is reflected at the set of variable acoustic elements labeled



FIG 2. The acoustic bridge held in its operating position. (From *International Audiology*)

matching impedance. If the reflections in both tubes are equal the resulting sound waves cancel each other out in the middle of the small tube bridging the transducer. Under these conditions, practically no sound can be detected in the output tube.

The set of variable acoustic elements consists of two volumes of air separated by a narrow slit. The first volume,  $V_1$ , simulates the ear canal and is adjusted to match the volume of each individual ear canal before the beginning of actual measurements. The volume is determined by filling the ear canal with alcohol with the help of a calibrated syringe. The second volume,  $V_2$ , supplies the acoustic compliance which is matched to the effective compliance at the eardrum. The narrow slit provides an acoustic resistance which can be made equal to the acoustic resistance at the eardrum. The measurement is executed by varying the volume  $V_2$  and the resistance  $R$  until the sound in tube 1 is minimized. When this is achieved the effective compliance and resistance can be read directly on the bridge dials. The variable compliance and resistance are mutually independent and can be adjusted within a minute or two.

The next slide (Fig 2) shows how the instrument is held in the ear. The black tube leads to the examiner's ears.

#### MIDDLE EAR FUNCTION

Let us now consider the functional anatomy of the middle ear which is shown in the following slide (Fig 3). In the normal ear the central por-

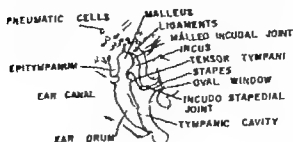


FIG. 3. Functional anatomy of the middle ear.

(From the Journal of the Acoustical Society of America.)

tion of the eardrum and the three ossicles vibrate nearly as one rigid body. At frequencies below about 500 Hz, this motion is controlled mainly by the compliance of the ossicular attachments and of the membrane of the round window. When the incudo-stapedial joint is severed the compliance measured at the eardrum is doubled. When the stapes is fixed the compliance decreases to about one half of the normal value. It does not go to zero because some relative motion occurs in the ossicular joints. Between 500 and 1500 Hz, the effective compliance of the middle ear system is enhanced by the mass of the ossicles. Somewhat above 1000 Hz, the compliance tends to become infinite in the normal ear. Ossicular separation brings the resonance point down to about 700 Hz. Stapes ankylosis shifts it toward higher frequencies.

The effective resistance of the normal ear decreases somewhat from low to high frequencies. Ossicular separation reduces it at low frequencies to less than one half. This is so because the main source of resistance, the cochlea, becomes disconnected. Stapedial ankylosis increases the resistance at low frequencies because of friction in the ossicular joints.

The greatest reduction in compliance at the eardrum occurs in the presence of massive adhesions to the malleus, since the malleolar umbo becomes immobilized and the only possible motion is confined to the peripheral portions of the eardrum. Under these conditions, the effective resistance tends to be very high.

## RESULTS OF ACOUSTIC MEASUREMENTS

The next slide (Fig. 4) shows median compliance and resistance values of normal and otosclerotic ears as well as of ears with ossicular separation. The compliance is plotted in terms of an equivalent volume of air ( $V_e$ ), the resistance in acoustic Ohms—but the absolute values do not interest us here. It is clearly evident that otosclerosis leads to a substantially reduced compliance and ossicular separation to a substantially increased compli-





GRAHAM-STEARNS COMPANY  
INCORPORATED, NEW YORK

NAME MEDIA 2  
AGE 30 SEX M  
DATE 1-15-57 BY ---

CANAL VOLUME  
RIGHT EAR --- RL  
LEFT EAR --- RL

PURE TONE SUBSTRATES



WITH E-ARM MUSCLE REFLEX  
RIGHT EAR --- RL  
LEFT EAR --- RL

COMMENTS

- O NORMAL (33 S)
- OTOSCLEROSIS (24 S)
- X OSSICULAR SEPARATION (4 S)

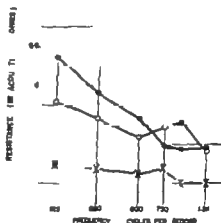
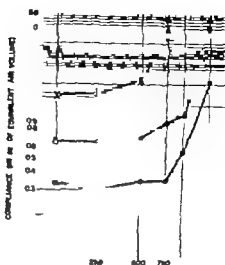


FIG 4 Median compliance (above) and resistance values (the audiogram) of normal, and otosclerotic, and ears with ossicular separation. The compliance is plotted on a logarithmic scale, the resistance on a linear scale. A standard clinical form has been used for this and the following plots.

ance. The resistance is somewhat increased in the presence of otosclerosis, and is clearly decreased by ossicular separation.

Maybe I should mention that the data are plotted on standard clinical forms which also include space for results of other tests. The compliance is plotted on a logarithmic scale, the resistance on a linear one.

Now I would like to show you some individual cases which may be of interest to you. The next slide (Fig 5) shows audiometric and acoustic results on a patient who was referred as a probable unilateral otosclerotic. The audiometric test shows a typical air-bone gap right and a normal hearing at low frequencies left. On the acoustic plots, the shaded areas indicate the ranges of 80% of ears with normal hearing. The compliance of the left ear fits neatly within this range; the resistance is just a little





ZWISLOCKI ACoustic BRIDGE  
COMPANY

ZWISLOCKI ACoustic BRIDGE  
MODEL SERIAL 23

NAME C. A.  
SEX M. RES. N.  
DATE 6/25/53 BY A. P.

CANAL VOLUME  
RIGHT EAR 0.00  
LEFT EAR 0.00

PURE TONE AUDIOMETRY  
(A.B.A. 1951)  

20	10	25	5	15	15
80	55	60	45	55	55

 250 500 Hz 1k 2k 4k 8k

BOULE  

0	15	20	15
5	10	20	10

 250 500 Hz 1k 2k 4k 8k

IMMEDIATE EAR IMPEDEANCE MEASUREMENTS  
 RIGHT EAR 0.00 1000 Hz 1000 Hz  
 LEFT EAR 0.00 1000 Hz 1000 Hz

COMMENTS

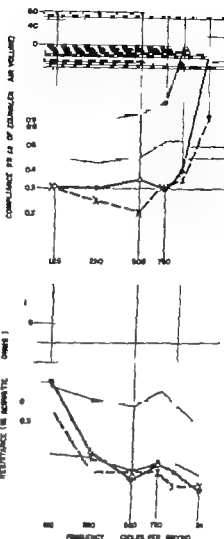


FIG. 6 Results of acoustic examination of a patient with asymmetrical otosclerotic ankylosis.

of unilateral otosclerosis and appears to indicate an early stage of stapedial fixation

If you looked only at the audiometric results of the next slide (Fig 7) you would probably conclude that you have a case of sensor neural hearing loss before you. However the acoustic compliance is drastically reduced, particularly in the left ear which has the greater hearing loss. The resistance is high. This pattern is consistent with massive adhesions to the incus or even malleus. Dr. Shea operated and found light otosclerosis accompanied by massive adhesions.

I don't have enough time for more individual cases, but I would like to show you some postoperative acoustic measurements. Dr. Feldman of the New York Upstate Medical Center had the opportunity to examine three small populations of patients with different types of stapedial prostheses. The next slide (Fig 8) shows the median compliance and resistance values

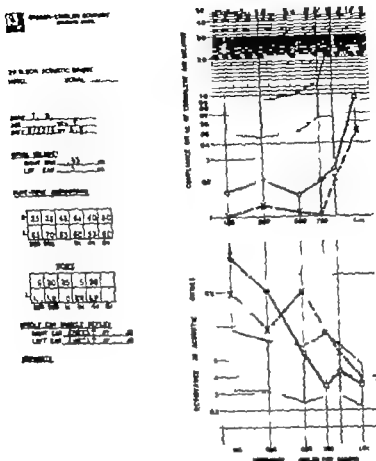


FIG. 7. Results of acoustic examination of a patient with otosclerosis and massi reflexion. Note the impedance and metric results.

he obtained. Both the wire fat and the teflon prostheses have produced a larger than normal compliance and smaller than normal resistance. This indicates a weakened coupling with the inner ear and could possibly account for some of the residual postoperative hearing loss. The stainless steel prostheses produced on the average approximately normal compliance and resistance values, but the resonance point seems to have been shifted toward the lower frequencies. This is consistent with an increased effective mass.

What I have shown you does not exhaust the applications of the acoustic method. Through detection of the acoustic muscle reflex, the method has been applied to cases of Bell's Palsy and to the determination of loudness recruitment. In conjunction with the Valsalva maneuver or similar procedures it also permits testing of the Eustachian tube.

The acoustic method is now being used at several clinics in this country



EMERSON-STROHLE COMPANY  
CHICAGO, ILL.

NAME MEDLIN  
AGE 35 SEX M  
DATE 5-5-63 BY JS

CARPH. VOLUME  
RIGHT EAR PS  
LEFT EAR PS

PURE TONE AUDIOMETRY



MIDDLE-EAR MUSCLE REFLEX  
RIGHT EAR AT  
LEFT EAR AT

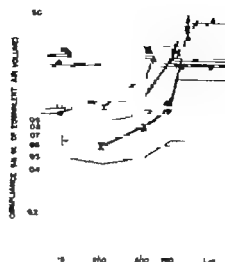
COMMENTS

PROSTHESES

O WIRE PAX (8 E)

TEFLOW (1 E)

X STAINLESS STEEL (11 E)



(PS)

REMARKS (IN ACQUST)

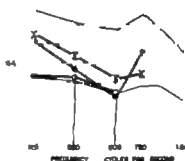


Fig 8 Medlin compliance and resistance of the eardrums of patient with middle ear prostheses.

and abroad. The next 10 or 15 years will show whether it will become accepted as a routine method of ear examination. This seems to be the average time lag between research and clinical practice.

## RESUME

La recherche acoustique récente qui emploie des instruments améliorés et l'analyse rigoureuse a amené une compréhension détaillée de la fonction normale et pathologique de l'oreille moyenne et une nouvelle méthodologie diagnostique. Cette méthodologie est complémentaire de l'audiométrie. Cette dernière est enrichie par l'application de quelques résultats de la recherche psychoacoustique sur les phénomènes de la sommation temporelle et de l'adaptation.

## ZUSAMMENFASSUNG

Kürzliche akustische Untersuchungen bei denen verbesserte Instrumente und genaue Analyse angewandt wurden haben zu einem recht detaillierten Ver-

Winkels der normalen und pathologischen Funktion des Mittelohrs und zu einer neuen diagnostischen Methodik geführt. Diese Methodik ergänzt die Audiometrie. Die letztere wird durch die Anwendung einiger Ergebnisse der psychoakustischen Untersuchungen über das Phänomen der Zeitintegration der akustischen Energie und der Adaptation erweitert.

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## DISCUSSION

F. Escher: What is the influence of the pneumatization of the mastoid on Mr. Zwislöcki's experiments? Especially in the case of total fixation of the ossicular chain as most admitted in tympanosclerosis, in which we find generally a lacking pneumatization.

F. Allmann: We have been using Mr. Zwislöcki's acoustic bridge in the Presbyterian Hospital for a while and find it an extremely useful diagnostic tool. I want to ask Dr. Zwislöcki if he knows of a method of temporarily loosening for the time of examination, perforation in the drum membrane so that the acoustic bridge could also be used in these cases before performing a tympanoplasty.

G. Lidin: In your presentation you mentioned that at 1000 Hz the middle ear is still compliant. From this point of view how do you feel about the choice of 500 Hz as a carrier frequency in the acoustic bridge developed by Møller and would you care to comment on this?

J. J. Zwislöcki (Reply): To Mr. Escher: The middle ear ossicles have little effect on the acoustic properties of the human middle ear at low sound frequencies. This is in contradistinction to conditions in the middle ear of small mammals where the acoustic properties at low frequencies are almost completely

determined by the air volume of the bulla. The compliance measured at the eardrum may be reduced drastically in pathologies other than tympanosclerosis. It is quite sensitive to adhesions to the large ossicles and even viscous fluid can bring it almost to zero.

to Mr. Allmann: Techniques of closing eardrum perforations are not my territory and I would be very reluctant in making any suggestions. We have never attempted to measure the acoustic properties of the middle ear in the presence of tympanic perforation. However, the compliance and resistance of the middle ear are not sensitive to eardrum properties and any light material placed over a portion of the eardrum should permit acoustic measurements without negatively affecting their results.

to Mr. Lidén: Möller's suggestion is to measure the acoustic reflex at 800 Hz. We have been using 750 Hz for similar determinations. In some ears, the change of acoustic properties due to muscle contraction is very strong in this frequency region. However, in other ears it is hardly noticeable. The reflex effect appears to be more stable at 250 and 500 Hz. As a consequence, we usually test it at two or three frequencies.

## ON COCHLEAR SHARPENING AND CROSS-CORRELATION METHODS

E. DE BOER, Ph.D and L. B. W. JOVONCKES, M.D

*From the Physical Laboratory Ear Nose and Throat Department  
Wilhelmina Hospital Amsterdam, The Netherlands*

Responses of single fibres in the cat's auditory nerve due to white-noise stimulation were recorded on magnetic tape. The stimulus and the series of action potentials (spikes) were subsequently analyzed with the help of an "average-response computer". Matters were arranged in such a way that the computer averages the noise-wave shape fragment during a certain period prior to each spike. In this way the causative phenomena behind the excitation of the auditory neuron reveal themselves and can be further analysed.

It is a well known fact that the cochlea is capable of a limited amount of frequency resolution. Low tones are directed at the apical end, and high tones at the basal end. At a given spot along the basilar membrane a tone of a specific frequency produces a maximal vibration amplitude. Tones of different frequencies give less amplitude at that point. For lower frequencies the amplitude goes down with about 10 dB per octave; for higher frequencies this is about 40 dB per octave (Fig. 1). At the level of the auditory nerve however things are different. One given fibre of this nerve can give rise to a sound provoked discharge (in the form of a more or less irregular series of action potentials or "spikes") but this depends on the frequency and intensity of the tone. A fibre is most sensitive to a particular frequency, the so-called characteristic frequency (C.F.). Frequencies lower than that need to be presented at higher intensity, about 30 dB/octave more. Frequencies above the characteristic frequency must be presented at considerably higher intensities before a response is obtained; the slope amounts to 100-400 dB/octave.

The cochlea and auditory nerve both have the property that the slope at higher frequencies is the steeper one. But there is no further similarity between the data. The auditory nerve is considerably more frequency-selective than the cochlea. Between the level of cochlear movements and the excitation of nerve pulses there must be a sharpening mechanism. That mechanism makes the frequency response sharper, providing a sharper cut-off for frequencies deviating from the characteristic frequency (Fig. 2).

It is a remarkable property that the slope at the high-frequency end of each tuning curve is very high, 100-400 dB/octave (by technical standards tremendously high). Technical filters have a cut-off slope of the order of



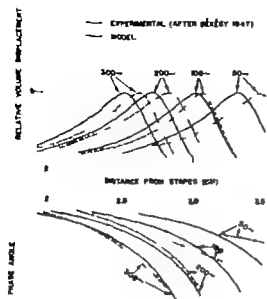


FIG 1



FIG 2.

FIG. 1. Frequency resolution in the cochlea frequency response at various points along the basilar membrane. From W. M. Møller (1962).

FIG. 2. "Tuning curve" of auditory neurons. The graph shows the frequencies (horizontal scale) and intensities (vertical scale) of all tones that give a threshold response. A tone outside the tuning curve gives no response. From Th. Weiss (1964).

0, 12, 18 or 24 dB/octave. It is rather difficult to make a filter that cuts off at a much faster rate.

On the problem of this cochlear sharpening mechanism a few theories are proposed. One is that the auditory nerve fibres, in their course along several hair cells of the organ of Corti, act as gates. They are supposed to pass a pulse only when a number of hair cells gives off an impulse in just the right time order. One may say that this process resembles the action of a synapse in the CNS, although no synapse is actually involved. A critical factor in this theory is also the speed of propagation of a pulse along the auditory nerve fibre from one hair cell to the other.

A second theory assumes that the stimulation of any hair cell is already a complicated affair. It is not simply the movement of the basilar membrane that stimulates a hair cell but a more complicated function. A hair cell is supposed to be subjected to a combination of forces, compressional and shearing. It is thought that a proper combination of influences can be the source of cochlear sharpening.

At present there is no reason to prefer one theory over the other. The point is that there have been no reports on the signals that propagate along the nerve fibres in their course from hair cell to hair cell. There is even insufficient knowledge on the number of hair cells that are connected to a given fibre.

In our laboratory this problem has been studied in a completely new

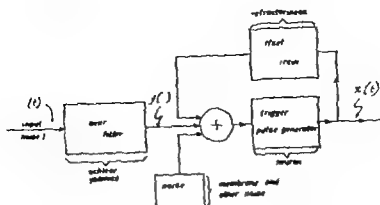


FIG. 3. Simplified model of auditory nerve excitation, after Th. Weiss (1964)

way. The method is a mathematical procedure that does not require access to an intermediate stage and yet gives information about the cochlear transformations (de Boer & Kuiper). Fig. 3 gives a simplified model of how we could assume an auditory neuron to be excited. The incoming acoustic signal is modified by cochlear filtering; a given location is maximally sensitive to a specific frequency.

Whenever the output signal surpasses a certain threshold, a nerve impulse is generated. To allow for spontaneous nerve spikes in the absence of acoustic input, an independent noise source must be introduced. The actual model is still more complicated but for our purpose this is sufficient. The problem is now that we should like to know more about the intermediate signal  $y(t)$  but we cannot reach this stage experimentally. Correlation theory now provides an answer. If one would stimulate the entire system with white noise, and if one could study the signal  $y(t)$ , then one could compute the cross-correlation function of  $x(t)$  and  $y(t)$ . In computing a cross-correlation function, a value  $x(t)$  is multiplied with the value  $y(t + \tau)$  taken seconds later. This is done for many values of  $t$  but with fixed  $\tau$ , and the resulting product is averaged over all time. The answer is a function of  $\tau$  that represents the average resemblance between values of  $x$  and  $y$  taken seconds apart in time.

If we now instead of  $x(t)$  and  $y(t)$  process  $x(t)$  and  $x'(t)$ —this being the train of nerve spikes—the result would be very much like the true cross-correlation function. That means that it is experimentally possible to derive the cross-correlation function (CCF) over the “cochlear filter” by processing on input and output signals of the entire system. There is an important theorem that says: for white noise stimulation the input-output CCF of a filter is equal to the filter’s “impulse response”. This is the output of the filter when the input is a very sharp impulsive signal. This all means that we are able, just by utilizing input and output of the cochlea, to find out all about the system labelled “linear filter” in the model.

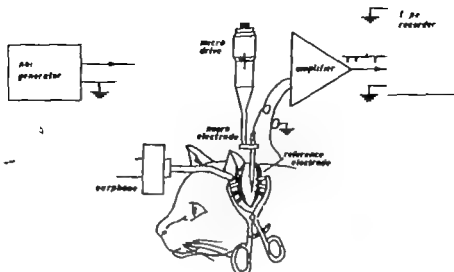


FIG. 4. Block diagram of the experimental set up.

The next figure (Fig. 4) shows the experimental set up. The cat's skull is opened, a portion of the cerebellum is sucked away and a glass microelectrode is inserted until contact is made with a neural unit in this case a primary auditory nerve fibre.

The animal's ear is stimulated with white noise, presented via an earphone. Both the white-noise stimulus and the ensuing train of nerve pulses are recorded on magnetic tape. Computation of a cross-correlation function generally is a quite complicated process. In this case it is much simpler: a computation run is done for each nerve spike; when no spike is present nothing need to be done. The computation is performed with help of an *average response computer*. Such a computer is able to determine the average waveform of an incoming signal. It must be set into action—synchronized—by a pulse.

When it receives a pulse it adds the incoming signal's waveform during a specified period to the waveform already present in the computer's memory. In the normal way of operation this instrument is capable of retrieving any average waveshape that is time-locked to the occurrence of synchronization pulses. This is possible even when the response is drowned in noise. In our case the computer is utilized in the *reverse* way. It is synchronized, not by the stimulus, but instead by the output of the preparation. The output—the series of action potentials—is converted into a series of neat pulses and these pulses synchronize the computer. After receipt of a pulse the computer is ready to process a signal. This signal is shown in Fig. 5.

On replay of the tape recorder we have two signals, the action spikes of the neuron and the input noise that caused them. As stated before the action spikes synchronize the computer. The input noise is fed to a second

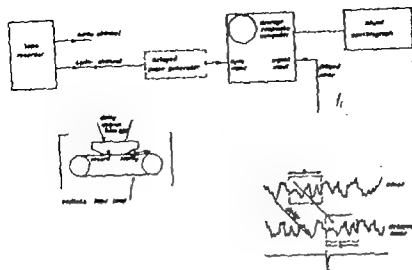


Fig. 8. Signal processing. The action spikes synchronize the computer. The white noise which originally causes them is delayed in time. The computer determines the average reshaped of the delayed noise over certain period after the spikes (see text).

tape recorder one that is provided with an endless loop of magnetic tape. Shortly after this white noise is recorded it is replayed, being picked up by a replay head on the recorder. In that way we have exactly the same signal again, but delayed in time.

What occurred earlier now appears at a later moment. Now suppose the computer is set into action by the receipt of a nerve spike and we give it the delayed version of the noise to act on. During a specified period after the action spike the computer adds this signal fragment to the waveshape in its memory. After a few thousand nerve spikes have occurred the computer has determined the average waveshape of the delayed noise. Or in other words, after all these nerve spikes have been processed, we have the average waveshape of the noise just prior to a nerve spike. It gives a picture of those portions of the stimulus that have—on the average—given rise to the action spikes. The function so computed, actually is the CCF of the input noise and the output spike signal. This function is a good representation of the cross-correlation function taken across the cochlear filter. (For the discussion of this point see de Boer & Harper.)

A representative example of the result of a computation is given in Fig. 8. It is the average waveform prior to a nerve pulse. The moment the nerve pulse occurs is at the left end.

It has an oscillatory waveform that damps out quite slowly. So this is about the shape of the CCF taken over the cochlear filter in our model. This, then, should also be the impulse response of the cochlear filter since white noise was given at the input.

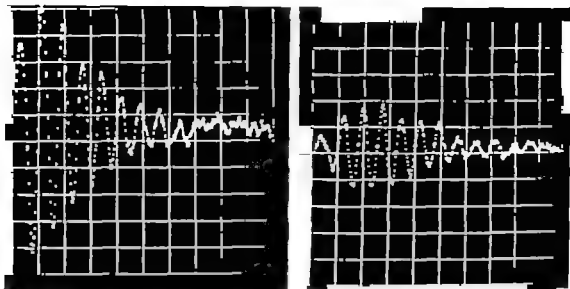


FIG. 6. Typical result of a computer simulation of the average waveform of a nerve pulse. CF of unit 1.7 kHz. Analysis time 7.5 ms. About 4000 spikes have been processed. The left-hand curve is taken at a 60 dB higher level than the right-hand one for the same unit.

We are now in a position to come back to the problem of cochlear sharpening. If our "cochlear filter" would be the same as the mechanism of cochlear dynamics we should know what the impulse response would be.

In Fig. 7 the impulse response that is valid for the movement of one particular spot on the basilar membrane is shown. It corresponds to the known type of cochlear filtering.

The experimental results, shown in the previous figure, are entirely different. They show much less damping and hence must correspond to a much sharper frequency filtering. As a matter of fact, further study has shown that the impulse response found corresponds to really very sharp filtering. The equivalent slope at the high frequency side ranges from 80 to 150 dB/octave for units with a CF of 500 Hz to 2 kHz. This is much higher than the slope for the cochlear frequency response. It comes close to the values found for the slopes of tuning curves. The value of 400 dB/octave pertains to units with very high characteristic frequency, too high to allow this type of processing. Units of lower CF have somewhat lower slopes. Actual values have not been measured, but the similarity is satisfactory so far.

What conclusions can we draw from this investigation? The first is that the model, as it stands, is a good model for the excitation of an auditory nerve fibre. Types of processing, other than those here described, failed to yield anything that contradicts our model. But the cochlear filter in the model does *not at all* correspond to the type of filtering that the cochlea is known to exhibit. It should be more sharply tuned, though still behaving like a linear network. Or better, like a quasi-linear network, i.e., the frequency-dependent part behaves like a linear filter (there may be some non

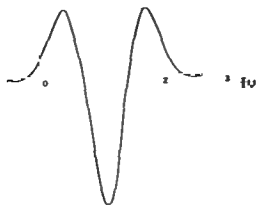


FIG. 7 Impulse response for one particular spot of the basilar membrane. From W. M. Siebert (1962). Note the normalized time axis.

linearities involved but these do not affect frequency resolution.) The next and ultimate question is how does this sharp filtering come about?

We have come much closer to answering this question. It is not possible that a neuron-like interaction in the cochlea causes the sharp frequency resolution found. Such a mechanism would be completely upset by giving it white noise as a stimulus. The interaction between hair cells must be of a more subtle nature. Two possibilities can be considered.

The first is that hair cells receive a complicated mechanical stimulation, which is so ordered that the right kind of frequency selectivity arises. The second possibility, not yet mentioned, resides in a different kind of interaction between hair cells. There has been doubt about the possibility whether the first part of a fibre can actually transmit pulses or not. One may suppose that it cannot do so; it can only transmit generator potentials by electrotonic spread. Only at the spot where the fibre acquires a myelin sheath can a nerve impulse originate. At that spot the influences of electrotonically propagated generator potentials add and when the sum surpasses the threshold, a nerve spike occurs. At the moment it is not possible to state which of these two possibilities is the most likely one. There are arguments in favour of both.

### CONCLUSION

The method used and described, essentially a correlation method, is an example of one of the modern systematic approaches to the analysis of compound systems. It is clear that, since in communication engineering many similar problems arise, we must keep a sharp eye on these developments. It may well be that in a completely unrelated field a problem is

solved by a method that is applicable to our problem. A team of specialists, not just one man trying to be universal is needed.

Such a team should include apart from the otologist, a physicist (or communications engineer) and, in our case a neurophysiologist. We were fortunate in having at our disposal all the required facilities in this respect as well as the people.

## RESUME

Les réponses évoquées par bruit blanc dans les fibres du nerf auditif du chat ont été enregistrées sur bande magnétique. Le stimulus et les séries de potentiels d'action ont ensuite été analysés à l'aide d'un "average-response computer". On a été arrangé d'une telle façon que le computer fait la moyenne des fragments d'ondes du bruit qui précèdent chaque potentiel d'action pendant une certaine période. Ainsi les causes de l'excitation du neurone auditif se révèlent et peuvent être analysées.

## ZUSAMMENFASSUNG

In Einzelfasern des Nervus acusticus bei der Katze wurden die von einem weissen Geräusch verursachten elektronischen Effekte auf Magnetophonband registriert. Der Reiz und die Reihe von Aktionspotentialen (Spikes) wurden dann analysiert mit Hilfe eines "average response computer". Die Aufstellung war derartig dass der Computer einen Mittelwert der Wellenform während einer gewissen Zeitspanne vor jedem Spike bildete. Die ursächlichen Phänomene der Reizung des akustischen Neurons zeigen sich in dieser Weise und können weiter analysiert werden.

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 With the help of the Medical Research Council  
 The N. S. Land*

## DISCUSSION

H. Davis: The problem attacked by Mr. De Boer and Mr. Jongkees is probably the most basic unsolved problem of cochlear physiology. The experiments reported give important additional information and we hope for a firm interpretation shortly. What is the range of frequencies for which such correlations with the stimulus have been established?

L. B. W. Jongkees (Reply): The frequencies one finds depend upon the neuron which is hit. They can be of various different characteristic frequencies. The method works for a CF up to over 2 kHz.

## ELECTRO-COCHLEOGRAMME HUMAIN EN DEHORS DE TOUTE INTERVENTION CHIRURGICALE

M PORTMANN M.D J M ARAN M.D et G LE BERT M.D  
Bordeaux, France

Les auteurs présentent des enregistrements des potentiels cochléaires (M. C. et P. A.) chez des sujets en dehors de toute intervention chirurgicale. Ils placent l'électrode au voisinage de la fenêtre ronde soit à travers une perforation du tympan lorsque celle-ci existe soit après paracentèse. Utilisant une stimulation par éléctrode, ils observent les réponses soit directement, soit après analyse de quelques dizaines de stimulations identiques et répétitives. Si les résultats obtenus chez les sujets présentant une perforation du tympan sont satisfaisants, il leur paraît difficile de placer l'électrode sur la fenêtre ronde dans les cas où le tympan est intact. Ils pensent cependant que en piquant un électrode sur le promontoire à travers le tympan il sera possible de mettre au point un électro-cochléogramme pour lequel l'utilisation et d'une stimulation répétitive par éléctrode et d'un moyen cur est indispensable.

Depuis la découverte par Weyer et Aran en 1930 de l'Effet Microphonique chez le chat les réponses électriques de la cochlée à une stimulation sonore ont abondamment été utilisées comme moyen de contrôle de l'activité cochléaire dans une grande variété d'expérimentations sur l'animal, depuis les recherches fondamentales sur le processus neuro-excitateur jusqu'au contrôle des manœuvres de micro-chirurgie, en passant par l'étude des différents agents oto-destructeurs.

Les deux principales réponses électriques observées dans la cochlée sont

1 le microphonique cochléaire (M. C.) signal dont la forme est, dans certaines limites, identique à celle du son lui-même,

2 le potentiel d'action nerveux (P. A.) réponse à une stimulation par éléctrode qui représente la somme des réponses cohérentes de l'ensemble des fibres nerveuses à l'intérieur de la cochlée.

Parallèlement à ces mesures chez l'animal, quelques essais ont été faits pour mesurer ces potentiels chez l'homme. Depuis 10 ans environ, grâce au progrès technologique des résultats de plus en plus intéressants sont obtenus, et ces mesures sont passées du stade de la recherche pure à celui des applications cliniques à ce en particulier les observations de Ruben *et al* et d'un grand différent en de l'audition (Ronsky, 1966 Ruben *et al* 1967 Ruben et W. Her 1963 Ruben, 1965).

Non à un point où de telles mesures seraient peut-être applicables à l'audiométrie. En effet le microchirurgien otologiste se trouve parfois devant des cas, certes rares, où il est délégué à décider d'une intervention chirurgicale sur l'oreille moyenne. L'audiogramme est difficile à interpréter.

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ter et l'on ne peut certifier que la surdité est d'origine interne ou de transmission. Dans ces cas là il est évident que si l'on pouvait disposer d'une indication précise sur le fonctionnement réel de la cochlée, la décision d'intervenir ou non sur l'oreille moyenne serait grandement facilitée.

Cependant l'enregistrement des réponses électriques de la cochlée chez l'homme présente deux difficultés majeures

- d'une part les réponses enregistrées au niveau de la fenêtre ronde sont très faibles et souvent masquées par le bruit de fond

- d'autre part les enregistrements réalisés par la plupart des chercheurs ont été faits au cours justement d'interventions chirurgicales sur l'oreille

Il va de soi que si on veut utiliser ces mesures pour l'audiométrie, il faut les réaliser en dehors de toute opération et sans trop de désagrément pour le patient

C'est ce que cette année, nous avons essayé de réaliser dans notre Laboratoire, mettre au point une technique permettant d'enregistrer les potentiels cochléaires en dehors de toute intervention chirurgicale et voir si l'on peut attendre, des réponses ainsi enregistrées, une indication valable sur le fonctionnement de la cochlée

## METHODES

### 1 Mode opératoire

Nous avons systématiquement essayé d'enregistrer les réponses cochléaires chez des sujets qui présentaient une perforation du tympan de telle sorte que la fenêtre ronde soit visible, puis, lorsque la méthode d'enregistrement des réponses n'a été au point, nous avons essayé, chez des sujets présentant un tympan intact d'introduire l'électrode à travers une micro-perforation réalisée après anesthésie locale

- Le sujet est allongé sur une table d'examen dans une pièce insonorisée et faradisée

- Un spéculum d'oreille est maintenu dans le conduit auditif externe au moyen d'une bande adhésive de telle sorte qu'il n'est solidaire que de la tête du sujet lui laissant ainsi une certaine liberté de mouvement

- L'électrode de masse est soudée au spéculum

- Sous microscope opératoire, l'électrode active est placée dans la niche de la fenêtre ronde. C'est un fil de Nickel-Chrome de 50 microns de diamètre dont l'extrémité est dénudée et aplatie

- L'électrode indifférente de même nature est posée sur le promontoire ou piquée dans le conduit auditif externe

### 2 Stimulation

Nous n'avons utilisé que la stimulation par clic, pour plusieurs raisons

- Le clic évoque à la fois une réponse microphonique et une réponse nerveuse qui sont facilement mesurables.

- En outre il est moins traumatisant pour l'oreille de stimuler aux fortes intensités, par un son très bref que par un son pur permanent

— De plus l'enregistrement des réponses à des sons purs de différentes fréquences et intensités aurait prolongé considérablement l'examen, mettant par trop à l'épreuve la patience du sujet.

— Enfin les réponses microphoniques à des sons purs sont faibles, et il est souvent difficile d'y discerner les réponses réelles des artefacts, en particulier du passage par influence du signal électrique de stimulation.

Certes une stimulation par clic ne peut donner d'indication sur la sensibilité en fréquence de la cochlée, mais, étant donné que les atteintes de l'oreille interne affectent principalement les aigus, c'est à dire se situent au premier tour de spire nous pensons que la présence de potentiel d'action aux faibles intensités et de microphonique et potentiel d'action aux fortes intensités sont des indications suffisantes sur le fonctionnement du premier tour voire de toute la cochlée.

— Le clic est donc produit (Fig. 1) par des impulsions rectangulaires de 0,1 ms de largeur qui, à travers des atténuateurs et un amplificateur Basse Fréquence, attaquent un moteur de haut parleur convenablement blindé. Le son est conduit alors à l'oreille du sujet à travers un tube souple terminé par un petit pavillon dont le diamètre est légèrement supérieur à la dimension de l'oreille externe. Celui-ci est, au cours de la stimulation, placé à un demi-centimètre de l'oreille. Cet espace est propre à atténuer considérablement la transmission du roulement résiduel.

Cet équipement a été calibré en décibels par rapport au seuil moyen d'audition du clic chez un certain nombre de sujets normaux. On peut ainsi obtenir des clics jusqu'à 140 db au-dessus du seuil.

### 3. Enregistrement des réponses

Les trois électrodes, active indifférente et masse sont reliées à un pré-amplificateur Tektronix à gain 1000 qui attaque d'une part une voie d'un oscilloscope C.R.C. à tube trace d'autre part, à travers un amplificateur supplémentaire une voie d'un enregistreur magnétique Ampex SP 300 (Fig. 1). La bande passant du pré-amplificateur est fixée

de 80 à 1000 Hz, quand on veut observer les réponses directement sur l'oscilloscope

de 8 à 10 000 Hz quand on veut les enregistrer sur l'Ampex.

Le synchronisation issue du générateur d'impulsions est envoyée sur l'oscilloscope et sur une autre voie de l'enregistreur magnétique. Enfin les commentaires sont enregistrés sur une troisième voie. Étant donnée la faible bande passant de l'enregistreur en modulation de fréquence nous avons préféré utiliser l'enregistrement direct. Le signal enregistré sur l'Ampex est simultanément lu et envoyé sur la deuxième trace de l'oscilloscope de façon à surveiller la qualité de l'enregistrement.

### 4. Mesure

Les réponses visibles sur l'oscilloscope pour différentes intensités sont aussitôt photographiées sur film Polaroid. On détermine assez difficile-

ter et l'on ne peut certifier que la surdité est d'origine interne ou de transmission. Dans ces cas là il est évident que si l'on pouvait disposer d'une indication précise sur le fonctionnement réel de la cochlée la décision d'intervenir ou non sur l'oreille moyenne serait grandement facilitée.

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## MÉTHODES

### 1 Mode opératoire

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— L'électrode de masse est soudée au spéculum.

— Sous microscope opératoire l'électrode active est placée dans la niche de la fenêtre ronde. C'est un fil de Nickel-Chrome de 30 microns de diamètre, dont l'extrémité est dénudée et aplatie.

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Nous n'avons utilisé que la stimulation par clic pour plusieurs raisons :

— Le clic évoque à la fois une réponse microphonique et une réponse nerveuse qui sont facilement mesurables.

— En outre il est moins traumatisant pour l'oreille de stimuler aux fortes intensités, par un son très bref que par un son pur permanent.



Fig. 2.

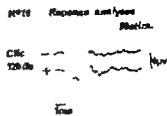


Fig. 3.

Fig. 2 et 3. Mise en évidence du changement de phase du microphonique cochléaire par rapport au potentiel d'action lors de l'inversion de la stimulation.

tion simultanée au clic d'un bruit blanc. Ce phénomène est très net, que le bruit blanc soit produit par un générateur électronique ou par un chuintement labial à l'oreille du sujet. Cet effet n'a pas encore été contrôlé sur l'Analyseur et une étude plus détaillée devra être entreprise.

Voici quelques exemples des réponses ainsi enregistrées chez certains sujets.

Sujet n° 22 (Fig. 5) l'oreille gauche présente une perforation que reflète bien l'écart des courbes de conduction osseuse (C. O.) et conduction aérienne (C. A.) la conduction osseuse étant relativement bonne. A partir de 110 db on obtient une très bonne réponse au clic, visible directement sur l'Oscilloscope. Grâce à l'Analyseur on voit qu'entre 80 et 90 db on a encore une réponse.

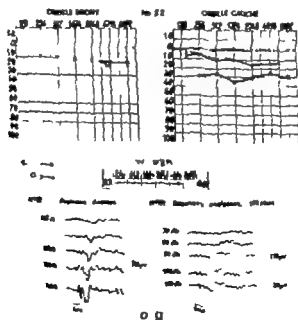


Fig. 5. Sujet 22 audiogramme et réponses enregistrées pour l'oreille gauche

ment certes, le seuil des réponses visibles sur l'oscilloscope. En partant alors de 40 db en-dessous de ce seuil, on réalise des séries de stimulations identiques à raison de 6 clics par seconde, les signaux correspondant étant enregistrés sur l'Ampex. L'on procède ainsi pour des intensités croissantes de 10 en 10 db jusqu'à l'intensité pour laquelle on a une réponse directe nettement visible à l'oscilloscope. Lorsque pour certains sujets, aucune réponse n'était bien visible directement on réalisait néanmoins l'enregistrement à des stimulations répétitives de 100 à 130 db.

Grâce à l'obligeance de l'entreprise « l'Electronique appliquée » qui réalise entre autre du matériel médical nous avons pu utiliser l'Analyseur Multicanaux « Elatron 1600 » pour analyser les réponses ainsi enregistrées chez une douzaine de sujets. Utilisant sa fonction moyennneur les signaux répétitifs sont additionnés de telle sorte que l'on peut extraire la réponse moyenne du bruit de fond dans laquelle elle était noyée.

## RÉSULTATS

En réponse au clic nous obtenons donc le microphonique cochléaire immédiatement suivi du potentiel d'action. Nous avons pu vérifier les caractéristiques classiques de ces réponses qui garantissent leur nature physiologique, que ce soit sur une réponse directe ou sur la sommation de nombreuses réponses dans l'Analyseur.

Ce sont

— l'inversion de la phase du microphonique cochléaire le potentiel d'action gardant le même sens négatif quand on inverse la polarité de la stimulation (Figs 2 et 3) (les réponses sont enregistrées de telle sorte que les pics négatifs sont dirigés vers le bas)

— la latence du potentiel d'action par rapport au microphonique entre 1 et 2 ms (Figs 2 et 4)

— l'augmentation de cette latence avec la diminution de l'intensité du clic (Fig 5 et suivantes)

— l'effet de masque produit sur le potentiel d'action par la présence

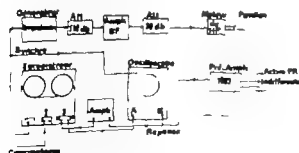


Fig. 1

Fig. 1 Schéma de l'appareil

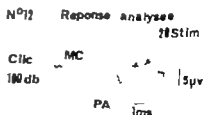


Fig. 4

Fig. 4 Exemple de réponse analysée chez le sujet n° 12

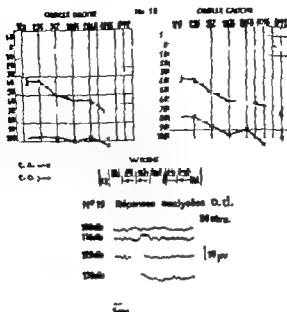


Fig. 7 Sujet n° 19 diagramme et réponses analysées pour l'oreille droite.

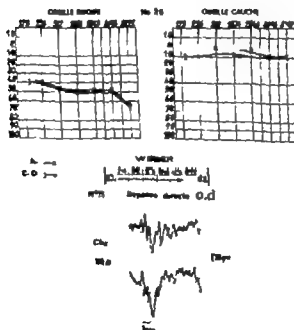


Fig. 8 Sujet n° 26 audiogramme — réponses clic à 100 db (+ et -) l'électrode près paracostée

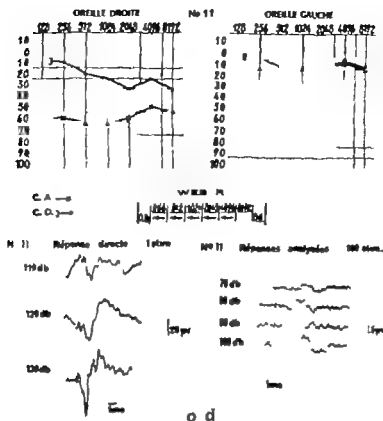


FIG 6 Sujet n 11 — audiogramme et réponse enregistrées pour l'oreille droite

L'ensemble des traces montre bien en outre la variation de la latence du potentiel d'action avec l'intensité de la stimulation

Sujet n 11 (Fig 6) l'oreille droite présente une perforation à laquelle s'ajoute une surdité de transmission et une chute en voie osseuse pour les aigus. Cependant on obtient encore de bonnes réponses et sur l'Analyseur on distingue encore une très légère réponse à 70 db

Sujet n 19 (Figs 4 et 7) forte surdité bilatérale à la fois de transmission et de perception

Pour l'oreille droite qui présentait aussi une perforation il était difficile de déceler une réponse directement sur l'Oscilloscope mais, à travers l'Analyseur les réponses sont nettes à 120 et 130 db, puis beaucoup plus faibles déjà à 110 db

Sujet n 26 (Fig 8) surdité de perception chute de 40 à 50 db pour l'oreille droite qui ne présentait pas de perforation aussi l'électrode a-t-elle été introduite, au voisinage de la fenêtre ronde à travers une micro-perforation réalisée dans le tympan. Malgré beaucoup de bruit de fond une bonne réponse directe est observée à 100 db, l'inversion du clic laissant inchangée la phase de la réponse nerveuse

Sur les 27 sujets que nous avons testés

— les premiers ont uniquement servi à mettre au point les méthodes de stimulation et d'enregistrement

## ZUSAMMENFASSUNG

Die Autoren untersuchen seit mehreren Jahren menschliche Elektrocochleogramme welche ohne irgendeine operative Behandlung registriert werden. Die 1947 von Bordenau veröffentlichte Methode gestattet die Aufnahme eines Elektrocochleogramms bei Kranken entweder mit perforiertem oder mit normalem Trommelfell. Die Ergebnisse werden in Verbindung mit besondern klinischen Fällen analysiert deren Knochenleitung mit der üblichen Methode der Audiometrie nicht in einwandfreier Weise untersucht werden konnte. Obgleich sie unergonomisch ist, unterstreichen die Autoren die Bedeutung einer solchen Methode für das Anzeigen gewisser chirurgischer Eingriffe.

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— Nous avons obtenu des réponses, plus ou moins importantes suivant l'audition du sujet et la qualité du positionnement de l'électrode, chez 16 sujets dont tous, sauf 2 présentaient une perforation

— Parmi les sujets pour lesquels nous n'avons pu obtenir de réponses 4 étaient pratiquement sourds totaux pour 4 des 8 sujets chez lesquels l'électrode était introduite après paracentèse du tympan, l'électrode n'a pu être mise en place correctement malgré plusieurs essais et les enregistrements étaient saturés de bruit enfin chez les autres sujets, un manque de coopération de leur part rendait impossible toute mesure

### CONCLUSION

L'enregistrement des réponses cochléaires chez les sujets présentant une perforation du tympan est relativement aisé en plaçant l'électrode dans la niche de la fenêtre ronde, et les moyens dont nous disposons actuellement permettent de les mesurer correctement

Par contre, il semble difficile de placer l'électrode sur la fenêtre ronde à travers une micro-perforation du tympan avec suffisamment de chance de succès. Lempert *et al* (1950) avaient, dès 1950 fait cette constatation lors qu'ils essayaient d'enregistrer par cette méthode, le microphonique cochléaire

Cependant il ne faut pas pour autant abandonner l'idée de réaliser un test audiométrique par l'observation des potentiels cochléaires. En effet, après nos propres recherches et les travaux de Yoashle *et al* (1967) (qui enregistrent la réponse nerveuse en plaçant une électrode dans le conduit auditif externe et additionnent un grand nombre de réponses dans un moyennneur) nous sommes certains que

— l'utilisation de la stimulation par elle

— la mise en place d'une électrode sur la fenêtre ronde quand cela est possible, ou bien systématiquement piquée sur le promontoire à travers une micro-perforation du tympan

— et surtout l'utilisation d'un Analyseur Moyennneur vont permettre la mise au point définitive d'un test « Electrocochléogramme » dont l'utilisation limitée à certains cas particuliers, sera d'un grand intérêt pour l'audiométrie

### SUMMARY

Within the last few years the authors have studied the human electrocochleogram recorded without a surgical procedure. This method published in 1967 in Bordeaux allows the recording of an electro-cochleogram on patients with either a tympanic perforation or a normal drum. These results are concerned with particular clinical cases on which the bone-conduction curve had never been accurately tested by routine audiometry. Though a exceptional the authors mention the interest of such a method especially as a help for indication for certain surgical operations.

## HISTOLOGICAL FINDINGS IN CONGENITAL DEAFNESS

F. ALTMANN, M.D.

*From the Department of Otolaryngology, College of P & S, Columbia University  
and the Presbyterian Hospital, New York City, N.Y., U.S.A.*

Histological findings in congenital deafness fall into two groups. The first group is characterized by changes resembling those observed in healed mild serous or viral labyrinthitis (maternal rubella) or in mild "posthydroptic neuroepithelial degeneration." The other group presents purely degenerative atrophic changes resembling to certain degree those of mild genetic neuroepithelial degeneration. The hypothesis is considered that the changes found in both groups could be the result of certain types of malnutrition of the stria vascularis which interfere with the ability of the stria to maintain the normal chemical constitution of the end lymph. This possible explanation is put forth in view of the similarities between the changes produced by genetic and the changes produced by extrinsic factors.

The anatomical findings in what is commonly called congenital deafness (i.e. deafness present at birth) can be divided into two groups: one group with regressive changes in the epithelial structures of the cochlear duct, the saccule and occasionally the utricle, their nerves, ganglia and central pathways, and another group with evident anatomical anomalies of the cochlea and sometimes also of the other parts of the inner ear.

The regressive changes characterizing the first group develop either "spontaneously" without any apparent extrinsic cause, or secondary to known extrinsic factors, such as virus diseases. "Spontaneous" regressive changes and outright developmental anomalies form the basis of genetically determined (inherited) deafness, "secondary" changes the basis of acquired deafness.

The majority of the malformations of the inner ear in genetically determined deafness are found without changes in other parts of the ear. Some of the inner ear malformations occur with the group of combined malformation of the external and middle ear known as atresia auris congenita. Others are observed in non-viable fetuses, associated with developmental anomalies of the central nervous system alone or combined with malformations of the external and middle ear.

Our knowledge of the spontaneous regressive changes is still limited. One group of cases, the so-called cochleo-saccular or Schelte type, is characterized by epithelial changes in the cochlear duct and its contained structures, the saccule and sometimes also their nerves, ganglia and their central

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## DISCUSSION

*II Davis* It is interesting to see how similar studies are made simultaneously on opposite sides of the world and how well the results agree. My former colleague Mr Yoshie now at Matsumoto in Japan has reported very similar experiments in the *Laryngoscope*. Mr Yoshie's technique differs in that he places the active electrode in the wall of the external auditory canal. He obtains good action potential responses to clicks but in a recent letter he writes to me that he has had much greater difficulty when he uses filtered clicks or tone bursts as stimuli.

*J E Bordley* I would like to express my appreciation and enjoyment of Mr Portmann's excellent presentation. The work on human cochlear responses to sound stimuli should be continued in order to give us as much information as possible on the activity of the functioning human peripheral endorgan in life.

Two remarks occurred to me while listening to Mr Portmann's essay. First the delay time between stimulus and the appearance of the nerve action potential as the intensity of the stimulus was increased appears to be shortened. This change in delay would seem reasonable but we have not recognized this in our results. We will be interested in looking for such changes in our future recordings.

After seeing the charts presented today the question arises if the essayist has noted a closer relation between the threshold of hearing and the appearance of the nerve action potential in severely hard of hearing patients than in the mildly deafened patient.

The use of computers in studies of cochlear potentials and nerve action potentials has proven much simpler in the latter. Much I am sure could be learned if we can develop better application of the computer to cochlear responses to pure tones.

*Mr Portmann (Réponse) à Mr Davis* Je peux répondre qu'effectivement Yoshie au Japon a publié un travail dans le *Laryngoscope* en même temps que nous dans la *Revue de Laryngologie*. Il sera intéressant de suivre les progrès de leurs méthodes.

*à Mr Bordley* Je peux dire que son commentaire était, pour moi important puisque son Service traite ces problèmes depuis 10 ans très activement. Nous n'avons pas trouvé de relation entre le niveau du potentiel d'action et le seuil subjectif. Cette relation ne nous a pas paru plus précise quand le malade était plus sourd mais d'autres data sont encore nécessaires.

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pathways. In another group of cases, in the so-called *Siebenmann Bing* type, epithelial changes are noted not only in the cochlear but also in the vestibular portion of the membranous labyrinth.

The histological findings in the *Scheibe* type are not uniform

In some observations the changes in the organ of Corti the stria vascularis and the macula sacculi are of a purely degenerative atrophic nature with collapse of Reissner's membrane and of the sacculle. They resemble, to a certain extent, those experimentally produced by Wittmaack by diffusion of a solution of acetic acid through the round window membrane into the inner ear and called by him "genuine neuroepithelial degeneration"

More frequently the degenerative changes in the organ of Corti and in the macula sacculi are associated with changes in the shape and position of the tectorial membrane which is either reflected backward over the crista spiralis or tucked into the internal spiral sulcus and is covered with a single layer of flat epithelial cells. The stria vascularis is atrophic but shows occasionally circumscribed papillary or fingerlike excrescences and contains, in rare instances, cysts. Reissner's membrane is frequently collapsed and adherent to the stria, rarely only bulging outward. Occasionally the lumen of the cochlear duct is traversed by thin strands of tissue. The sacculle is as a rule collapsed.

In both sub-groups of genetically determined deafness PAS positive deposits of unknown significance are frequently found in the stria vascularis and within the epithelium of the macula sacculi.

The changes in the second sub-group show a strong resemblance to changes which originally were regarded as characteristic for a healed mild serous labyrinthitis, secondary to an infection of the middle ear or of the meninges. However they were also experimentally produced by Wittmaack by introducing certain chemical substances, such as calcium chloride into the middle ear and letting them diffuse through the round window membrane into the fluids of the inner ear and called by him posthydropic neuroepithelial degeneration. Recently they have also been found in virus diseases of the inner ear particularly after maternal rubella in the first trimester of pregnancy. In the absence of a well documented history the differentiation between these different types of changes sometimes becomes very difficult. However in none of the so far reported cases of virus endolabyrinthitis have concretions in the stria vascularis or the macula sacculi been found or has a hydrops been demonstrated.

The similarity between certain changes in cases of genetically determined deafness of the cochleosaccular type and those in healed serous labyrinthitis of a mild degree including cases of virus endolabyrinthitis, has for a long time been puzzling.

It is well known that lesions brought about by the action of genes may be closely duplicated by a variety of unfavourable extrinsic factors (so-called phenocopies). The possibility therefore exists that in some cases of

congenital deafness where the hearing loss has no genetic basis, the loss may be due to an unfavourable environmental factor. According to Bosher & Hallpike (1965) it would seem likely that in the course of the maturation process the endolymphatic system has to pass through certain critical phases. They in themselves are liable to constitute an unfavourable environment which in combination with an unfavourable gene might bring about a form of cochleo-saccular degeneration. It is conceivable that viral damage to the developing stria might act similarly to a "genetic weakness" interfering with the ability of the stria to maintain the normal chemical constitution of the endolymph in the developing cochlea.

An analysis of the histological findings in hydrops of the labyrinth, regardless of its cause, leads to the conclusion that one of the first changes is a disruption of the attachments of the tectorial membrane to the various parts of the organ of Corti with subsequent retraction of the membrane. The retraction and the change in the shape of the membrane on cross sections from bandlike to globular could be explained by the assumption that it is elastic and stretched over the organ of Corti and that possibly after the attachments are broken, the membrane shrinks and tends to assume a shape with the smallest circumference. The retraction of the tectorial membrane might also facilitate penetration of the endolymph into the subreticular space and into the spaces normally filled with "Corti-lymph". The mixing of the two fluids might cause degenerative changes in the organ of Corti, particularly in the hair cells.

The group with evident anatomical anomalies of the inner ear shows changes not only of the contents of the cochlear duct and of the sacculus but also of the osseous framework of the cochlea. Siebenmann named these cases (*typus Mondini*) because they resemble the case first macroscopically described by Mondini (1791). In all of them both sides are affected. In the fully developed form the bony capsule of the cochlea is flattened from the base to the apex and the normal arrangement of the scalae is present only in the basal cochlear turn where the septum between the lower basal and middle turn is present. In the upper parts the intercalar septa are absent and a scala communis or cloaca is formed. The modiolus and the spiral laminae also show defects of varying degree. The cochlear turns are often reduced to 2 or even 1. The cochlear duct is in some instances markedly dilated, either along the entire course or in its upper parts only. In other cases the duct is collapsed. The sacculus, the endolymphatic duct and sac are almost invariably the utricle occasionally dilated. The membranous canal is as a rule normal. The organ of Corti is usually absent in part of the duct particularly in the more malformed upper region and is reduced to a flat mound of more or less undifferentiated cells in other parts. In some instances it shows typical "posthydropic" changes. The stria vascularis and the ligamentum spirale are often somewhat atrophic. Frequently the spiral ganglion presents a reduction in the number of the ganglionic cell and nerve fibers belonging to the more affected upper part in



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## DISCUSSION

I. Friedman: I have enjoyed this classical but somewhat disturbing presentation. The limitations of morphology are well known and the difficulties, technical and interpretive, well known. Yet the morphologist must continue to try to demonstrate certain morphological features and correlate them with the associated syndromes and possibly with the probable underlying causal mechanism.

Demonstration of three sections demonstrating PAS-positive deposit in the stria of a child who died suffering from the cardiovascular syndrome (Lange Nielsen and Jernell, 1957; Friedmann, Frogatt & Fraser 1963, *J. Laryngology*). Also electro-photograph of feet of neomycin on macula of the guinea-pig (Friedmann, Dodson & Bird 1966, *J. Pathology & Bacteriology*).

V. Tarok: The hypothesis is that the ultimate cause of function loss is the invasion of endolymph into the cortilymph, causing the loss of cochlear function. How can the vestibular function loss be explained? Most of the condition is responsible for developmental or degenerative inner ear disease, re-causing similar to total paralysis of the vestibular or the cochlear system.

F. (Friedmann) (Reply): I. M. Friedman: I did not mean to say that we will never be able to histologically differentiate various types of disease entities. However, I do not think that it is possible at the present time. On the other hand, the possibility is that the inner ear reacts to various intrinsic and extrinsic stimuli in an identical way. The PAS-positive concretions are erythrocytes because they have so far only been found in genetically determined and not in acquired deafness. An explanation can be given for it at the present time.

V. Tarok: I am unable to give an explanation for a loss of vestibular responses in certain cases of inherited deafness. The histological change are usually confined to or much more marked in the pars inferior. The physiology of the labyrinthine fluid in the pars superior is much less understood than that in the pars inferior.



rare instances it is completely absent. In other cases the ganglion is situated in the central parts of the modiolus and in the fundus of the internal auditory meatus. Changes in the primary cochlear nuclei were reported in some cases. Although the majority of the changes are unquestionably the direct result of an abnormal development, the "posthydropic" epithelial changes could have been brought about indirectly by the same mechanism as in the cases of the first group by a genetic weakness of the stria vascularis which interfered with its ability to maintain the normal chemical composition of the endolymph in the developing cochlea. The anomalies of the mesenchymal parts in these cases are probably to a certain extent dependent on the degree and nature of the malformations of the ectodermal parts. It should however be kept in mind that minor anomalies in the mesenchymal parts of the cochlea are often found in the absence of anomalies in the epithelial or nervous elements.

### RESUME

Les observations d'organes sensoriels en cas de surdité déterminée génétiquement se divisent en deux groupes. L'un est caractérisé par des changements qui ressemblent à ceux que l'on observe dans les labyrinthites séreuses ou virales guéries (rubéole maternelle) l'autre dans une dégénérescence neuroépithéliale posthydropique bénigne. Il y a des analogies entre les changements causés par les facteurs génétiques et par les facteurs extrinsèques. On peut considérer l'hypothèse que tous ces changements pourraient être le résultat d'un désordre de la strie vasculaire. Ce désordre empêcherait de maintenir la composition chimique normale de l'endolymphe.

### ZUSAMMENFASSUNG

Bei genetisch bedingter Taubheit können an den Endorganen zwei Arten von Befunden erhoben werden. Die eine Art ähnelt den Befunden bei leichtgradiger seröser Labyrinthitis, bei Virus Endolabyrinthitis (nach mütterlicher Rubella) oder bei leichtgradiger posthydropischer Neuroepithel Degeneration. Die andere Art zeigt rein degenerativ-atrophische Veränderungen die an die bei der genuine Neuroepithel Degeneration erinnern. In Anbetracht der Ähnlichkeit der Befunde bei genetisch bedingter und bei durch äussere Einflüsse verursachter Taubheit wird die Möglichkeit in Betracht gezogen dass alle diese Veränderungen letzten Endes auf eine gestörte Funktion der Stria vascularis zurückgeführt werden können. Die geschädigte Stria kann dann die normale chemische Zusammensetzung der Endolymphe nicht mehr aufrechterhalten.

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## MATERIALS AND METHODS

*Experiment I Effect of Sodium Fluoride on Tissue and Organ Cultures of Human Osteosclerotic Bone*

Surgical specimens of osteosclerotic bone were each divided in two pieces one always being a control, the other being cultured with sodium fluoride.

Some of these pieces were put into standard Rose chambers under tissue culture conditions with a media consisting of 85% Medium 199 and 15% Calf Serum. Time lapse studies were done on these.

Organ culture conditions were produced for the other specimens by (1) Rose chambers modified by the use of cellophane strips on both sides of the specimen, and (2) Roller tubes. Two media were employed the first being the same as that used for tissue culture the second being the media described by Biggers *et al* (1961).

Sodium fluoride in strengths of 1 to 15 ppm was used in the media for one half of each specimen. Tetracycline HCl (5, 10, or 25  $\mu\text{g}/\text{ml}$ ) was put in all the media.

*Experiment II Effect of Sodium Fluoride on Heparin Induced Osteoporosis*

Sprague-Dawley strain of rats were used, each litter with their nursing mother comprising one test. Each litter of 8 (or a comparable number) was divided into two groups 4 babies who received sodium fluoride in some form from birth and 4 who did not. The first 4 received daily intraperitoneal injections of 0.002 mg sodium fluoride for the three weeks prior to weaning. For the next 12 weeks they received 10 ppm sodium fluoride in their drinking water. At the age of 9 weeks each of the groups was further subdivided, half of each receiving heparin (Liquamin Sodium) subcutaneously three times daily for a total of 400 units per day for four weeks. The other half did not receive it. This now gave us four groups:

- A Control
- B Heparin
- C Sodium fluoride
- D Heparin and sodium fluoride

During the period of nursing, the mother was injected intraperitoneally daily with 5 mg tetracycline. After weaning, the babies all got 10 mg each in the same way. Thirteen weeks after birth the experiment was terminated. When using heparin, special care had to be taken of the animal because of the risk of bleeding.

Calvaria, humerus, radius, ulna, femur tibia, and fibula were dissected

The author gratefully thanks Dr. George G. Rose for the modification suggested. Dr. Petruskevicius gave personal help.

## STUDIES OF SODIUM FLUORIDE EFFECTS

(a) On Human Otosclerotic Bone

(b) On Prevention of Experimental Osteoporosis in Rats

(c) Synergistic Action with Phosphates

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In newborn rats, NaF in optimal doses promotes bone calcification both by decreasing bone resorption and stimulating calcium deposition. Sodium fluoride also has a preventive action on heparine-induced cortisone-induced and fracture-induced osteoporosis in 6- to 8-week-old rats, especially if given both before and after experimental fracture and combined after fracture with  $\text{Na}_2\text{HPO}_4$  and  $\text{KH}_2\text{PO}_4$ . Both the above results were observed by the semi-quantitative evaluation of tetracycline labeling vs. microchemical calcium assays.

### INTRODUCTION

Long term administration of large doses of heparin (Griffith *et al* 1965) and of cortisone (Stahl & Gvestner 1960 Goldsmith & Stahl 1953) have been shown to bring about osteoporosis.

On the other side clinical studies have suggested that sodium fluoride might have a beneficial effect in bone resorptive diseases such as osteoporosis (Rich & Ensick, 1961) and Paget's disease (Purves, 1962). Clinical studies have also indicated that phosphatesupplemented patients with fractures had an attenuated demineralization in the immobilized limb as compared to the non supplemented patients (Goldsmith *et al.*, 1967).

This paper concerns the effect of sodium fluoride on human otosclerotic bone in organ culture and the prevention of heparin and cortisone induced osteoporosis in rats. The synergistic action of sodium fluoride and certain phosphates will also be considered as well as their possible use for the active otoporotic stage of the disease process known as otosclerosis. It will be presented in three parts.

- 1 Materials and methods.
- 2 Experimental results
- 3 Discussion

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peared early and was very exuberant. Its fibroblast like cells ranging from 30 to 80  $\mu$ . The more mature lesion produced a less intense outgrowth with smaller (25 to 45  $\mu$ ) osteoblast-like cells. The latter were round in shape, with eccentric nuclei, and high Alkaline Phosphatase content. Time-lapse photography of the cells of both types of outgrowths showed the characteristic movements of their representation.

When these outgrowths were treated with sodium fluoride, we could not detect any significant effect. But with concentrations of sodium fluoride up to 15 ppm no deleterious effect on human osteosclerotic cell growth and proliferation or on the cytoplasmic movements (as analyzed by time-lapse microcinematography) were detected either.

Our next step was an attempt at growing the osteosclerotic surgical specimens under organ culture conditions. Each specimen was divided in two, with tetracycline given to both to detect new bone formation by a characteristic fluorescence under ultraviolet light. The medium of only one half of each piece contained sodium fluoride in order to detect its effects on calcification. Figs. 1 and 2 show two halves of a surgical specimen of osteosclerotic bone. Tetracycline fluorescence is both more intense and spread over a wider area in the half with sodium fluoride. This means that in organ culture sodium fluoride *does* have a promoting effect on calcification of osteosclerotic bone.

#### *Experiment II Effect of Sodium Fluoride on Heparin-Induced Osteoporosis*

Between groups A (control) and C (sodium fluoride) there was no significant difference in UV-induced fluorescent intensity (see Fig. 3). C was possibly brighter than A, but only marginally. In those bones treated with heparin, group B (heparin alone) was much lighter than D (heparin with sodium fluoride). If these groups were placed in a line of decreasing intensity the order would be as follows: C-A-D-B.

From our previous research on rats we have found that tetracycline is deposited at the same time as the calcium of bone formed during its administration. The more calcium deposited the more tetracycline also deposited and therefore the greater fluorescent intensity. This has been double-checked by microchemical spectrophotometric assays of calcium (Leirovic *et al.* 1966). The validity of a semi-quantitative estimation of calcium deposition was confirmed by studies of endochondral ossification of the anterior extremity of Meckel cartilage (Petrovic & Shambaugh, 1966; Leirovic *et al.* 1966).

In the light of this previous study we can interpret our results to see that group B (heparin, but no sodium fluoride) had the least amount of calcium compared to the group getting no heparin. Group D (heparin and sodium fluoride) too had a lower amount, but not as small as that of B. From this we can see that the difference in fluorescent intensity is greater

and divested of all non bone material. They were then photographed under ultraviolet light in the following pattern for an easy comparability.

		Heparin.	
		No	Yes
Sodium fluoride	No	A	B
	Yes	C	C

Ten litters were thus examined.

The method of photography was the same as that detailed in a previous paper (Petrovic & Shambaugh 1966).

*Experiment III Effect of Sodium Fluoride and Sodium Phosphate dibasic ( $\text{Na}_2\text{HPO}_4$ ) and Potassium Phosphate monobasic ( $\text{KH}_2\text{PO}_4$ ) on Cortisone induced Osteoporosis*

Sprague Dawley rats were again used and tetracycline given as in the heparin experiments. Twelve litters were examined.

The chart below details the time and dosage of sodium fluoride, cortisone acetate and phosphates given to litters of 12 rats. There are six groups within each litter, each group consisting of 2 rats. The first group is a control group receiving only tetracycline.

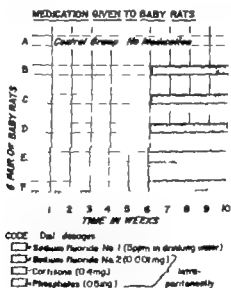


FIG. 1. Ham 1 xel rot1 footplate cultured with tetracycline for 10 days.

### Experimental Results

*Experiment I Effect of Sodium Fluoride on Tissue and Organ Cultures of Human Osteosclerotic Bone*

We found with the tissue culture methods that normal stapes footplate did not give rise to any significant cell outgrowth, but the osteosclerotic footplate did. When the lesion was immature and active, the outgrowth ap-

peared early and was very exuberant. Its fibroblast like cells ranging from 30 to 80  $\mu$ . The more mature lesion produced a less intense outgrowth with smaller (25 to 45  $\mu$ ) osteoblast-like cells. The latter were round in shape with eccentric nuclei, and high Alkaline Phosphatase content. Time-lapse photography of the cells of both types of outgrowths showed the characteristic movements of their representation.

When these outgrowths were treated with sodium fluoride, we could not detect any significant effect. But with concentrations of sodium fluoride up to 15 ppm no deleterious effect on human osteosclerotic cell growth and proliferation or on the cytoplasmic movements (as analyzed by time-lapse microcinematography) were detected either.

Our next step was an attempt at growing the osteosclerotic surgical specimen under organ culture conditions. Each specimen was divided in two, with tetracycline given to both to detect new bone formation by a characteristic fluorescence under ultraviolet light. The medium of only one half of each piece contained sodium fluoride in order to detect its effects on calcification. Figs. 1 and 2 show two halves of a surgical specimen of osteosclerotic bone. Tetracycline fluorescence is both more intense and spread over a wider area in the half with sodium fluoride. This means that in organ culture sodium fluoride *does* have a promoting effect on calcification of osteosclerotic bone.

#### *Experiment II: Effect of Sodium Fluoride on Heparin Induced Osteoporosis*

Between groups A (control) and C (sodium fluoride) there was no significant difference in UV induced fluorescent intensity (see Fig. 3). C was possibly brighter than A, but only marginally. In those bones treated with heparin, group B (heparin alone) was much lighter than D (heparin with sodium fluoride). If these groups were placed in a line of decreasing intensity the order would be as follows: C-A-D-B.

From our previous research on rats we have found that tetracycline is deposited at the same time as the calcium of bone formed during its administration. The more calcium deposited, the more tetracycline also deposited, and therefore the greater fluorescent intensity. This has been double-checked by microchemical spectrophotometric assays of calcium (Petronic *et al.* 1966). The validity of a semi-quantitative estimation of calcium deposition was confirmed by studies of endochondral ossification of the anterior extremity of Meckel's cartilage (Petronic & Shambaugh, 1966; Petronic *et al.* 1966).

In the light of this previous study we can interpret our results to see that group B (heparin, but no sodium fluoride) had the least amount of calcium compared to the group getting no heparin. Group D (heparin and sodium fluoride) also had a lower amount, but not as much as that of B. From this we can see that the difference in fluorescent intensity is greater

between non heparin and heparin treated bones when they had received no accompanying sodium fluoride than when sodium fluoride was given. In this case the difference between heparin and non heparin treated bones was less, indicating that sodium fluoride had in some way significantly hindered the osteoporotic effect.

We went one step further and checked the parathyroids of the animals treated in this experiment. Goldhaber (1965) has shown that in tissue culture heparin enhances the amount of bone resorption obtained with parathyroid extract or other factors which stimulate bone resorption. We want to emphasize that our cytological and cytochemical study of the parathyroid did not lead to the detection of any stimulation of parathyroid by the use of heparin. In other words, the action of heparin on bone seems not to be mediated through the parathyroids.

### *Experiment III Effect of Sodium Fluoride and Sodium Phosphate dibasic ( $\text{Na}_2\text{HPO}_4$ ) and Potassium Phosphate monobasic ( $\text{KH}_2\text{PO}_4$ ) on Cortisone induced Osteoporosis*

The UV induced tetracycline fluorescence seen in the bones of the litter mate rats grouped from A to F (see above—Materials and Methods) permit

FIG. 2. Portion of same footplate Fig. 1 cultured with tetracycline and 5 parts per million of sodium fluoride in the culture medium. The much greater fluorescence in Fig. 2 indicates greater calcium deposition during 8 days of culture as a result of sodium fluoride either promoting calcium deposition or reducing resorption—a combination.

FIG. 3. Tibia and fibula of rat littermates that received the following: (a) Upper left, adult cross, control receiving tetracycline only from the 1st to the 13th week after birth; (b) Upper right, litter mate rat receiving tetracycline 1st through the 9th week, tetracycline and 400 units of heparin daily 10th to the 13th week, showing heparin-induced osteoporosis; (c) Lower left, rat receiving tetracycline 1st to the 3rd week, tetracycline and 10 parts per million of sodium fluoride in drinking water 4th to the 13th week; (d) Lower right, rat receiving tetracycline 1st to 13th week, with sodium fluoride in the drinking water 4th to 8th week, heparin, 300 units daily 10th to 13th week, showing protection against heparin-induced osteoporosis as a result of sodium fluoride.

FIG. 4. Leg bones of rat littermates: (a) Upper left, rat receiving tetracycline only 1st through 10th week; (b) Middle left, rat receiving tetracycline plus 0.4 mg cortisone from 7th to 10th week, showing cortisone-induced osteoporosis; (c) Lower left, same medication but with 0.5 mg phosphates added 7th to 10th week, showing osteoporosis not significantly reduced by phosphates; (d) Upper right, rat receiving tetracycline 1st to 10th week, with cortisone 0.4 mg daily 3 parts per million sodium fluoride in drinking water added 7th to 10th week. Slight protection against cortisone-induced osteoporosis compared to (b); (e) Middle right, rat receiving tetracycline 1st to 10th week, with cortisone, sodium fluoride, and phosphates added 7th to 10th week, showing reduced cortisone-induced osteoporosis; (f) Lower right, same experiment as (e) but with sodium fluoride added 1st to 6th week plus 4th to 6th week plus tetracycline and cortisone. Here the maximum protection against cortisone-induced osteoporosis is seen with no difference in the fluorescence compared to control (a).







the following relationships. Osteoporosis is blatantly evident in group II its calcium content is enormously diminished from the amount seen in the control group A. There was no observable significant difference between the bones of II (cortisone) and C (cortisone and phosphates simultaneously) B and C both show the least amount of fluorescence, i.e. the least amount of calcium. The osteoporosis of B was not significantly hindered by the addition of phosphates alone as seen in C. A slightly greater calcification was evident in D (cortisone and sodium fluoride simultaneously) but we have seen before that sodium fluoride promotes calcification, so this would be expected. When in E, phosphates, sodium fluoride, and cortisone were all given at the same time even more calcification was evident by another increase in fluorescence. Since phosphates alone seem to produce no detectable effect, a synergistic action between sodium fluoride and phosphates seems to be indicated. The optimum conditions to prevent cortisone induced osteoporosis are evident in group F where sodium fluoride was given before cortisone and then sodium fluoride cortisone and phosphates were given simultaneously. That this interaction was the optimum can be easily seen when group F shows the same amount of fluorescence as A—the control. Timing the treatment thus completely negated the osteoporotic effect of cortisone. Calcium deposition occurred at the same rate as in the untreated control and there was no significant increase in resorption. We must mention that even under rigorous experimental conditions, we often observed some quantitative differences from litter to litter.

Experiments now under way confirm that the best way to hinder and at times actually prevent osteoporosis, is to administer the sodium fluoride for prolonged periods before the heparin intake and then to give sodium fluoride with phosphates afterward.

## DISCUSSION

First, we would like to emphasize the following methodological point. We do not state that the differences in the fluorescent intensity of tetracycline result exclusively from the differences in the deposited calcium amount; other factors may be causative. But, our previous experiments have shown that when there is intense bone depositing activity—either alone or combined with bone remodelling—then the great differences in fluorescent intensity do relate to the amounts of calcium deposited.

The validity of the tetracycline labeling method was in fact upheld when in a earlier paper (Petroyck *et al.* 1966) we showed that when there is more calcium, there is a higher fluorescent intensity. We knew that tetracycline was good for a semi-quantitative estimation of calcium amounts, but we needed a microchemical analysis by a spectrophotometric method of the exact amount of calcium present in the bones after various sodium fluoride doses. The first such a study was done on newborn rat parietal

bones and the results have shown a definite corroboration of sodium fluoride's promoting effect on deposited calcium (Petrovic & Shambaugh, 1966). A marked difference in effect is seen between the two doses: the strong dose does not give as good an effect as does the optimal. This relates exactly to the differences in tetracycline fluorescence.

As tetracycline was given from the beginning to the end of the experiments reported in this paper, we do not know what part is due to deposition and what part is due to resorption—but we do know the overall result. This was done purposely in an effort to reproduce in animals the human clinical situation.

As used in our experiments, the technique employed appears valid in which case our results, as reported above, show that sodium fluoride may hinder or entirely prevent heparin or cortisone induced osteoporosis.

The problem then arises: What are the possible mechanisms involved in this sodium fluoride action? We do not here wish to discuss this important problem at length. However, we will mention two of our previous experiments which give some insight into the possible mechanisms involved.

Our previous investigations (Petrovic & Shambaugh, 1966; Petrovic *et al* 1966) have shown that sodium fluoride certainly brings about a reduction in bone resorption and most likely brings about a promotion in bone calcification. To analyze this further, we did an organ culture study of previously sodium fluoride-enriched bone, specifically checking the osteoclasts after parathormone-induced resorption (Petrovic *et al* 1967). Tetracycline fluorescence showed us that the bone trabeculae with a higher sodium fluoride content underwent a less intense parathormone induced resorption. Radioautographic studies using  $H^3$ -cytidine and  $H^3$  leucine incorporation showed that the osteoclasts seem to have a lower functional activity when the bone trabeculae undergoing resorption had a higher fluoride content. This lessening of osteoclastic functional activity could be a result of either a decreased proneness of the sodium fluoride richer bone trabeculae to be resorbed or an increased localized concentration of fluoride consecutive to the local release of fluoride during bone resorption. Of course it could be a result of both.

A new series of organ culture experiments was set up to find out whether there was an action on calcium deposition itself. For this we studied the incorporation of  $Ca^{45}$  into the 18-day-old mouse embryonic ulna, both with normal and sodium fluoride-plus media. Results clearly show that the amount of  $Ca^{45}$  incorporated in organ culture into the ulnae was significantly higher when sodium fluoride was added to the medium. These experiments were designed specifically to see whether there is stimulation of  $Ca^{45}$  uptake from sodium fluoride. We realize that even in embryonic bone resorption may be occurring. In any difference of  $Ca^{45}$  between treated and untreated explants we cannot exclude the possibility of resorption occurring, simultaneously with deposition. However, because of the very short term of the experiments and the embryonic age of the specimens used, we believe

we can safely conclude that the bulk of the difference must be due to an increased calcium deposition. What is irrefutable is that the total amount of incorporated  $\text{Ca}^{45}$  has been increased, whatever the mechanism.

One last word related to heparin induced bone resorption concerns investigations now in progress on hibernators. We have observed that those bones undergoing, during the winter sleep, a more intense resorption contain at the same time more mastzellen cells known to secrete heparin.

### CONCLUSIONS

1 In tissue culture normal stapes produce no significant cell outgrowth young active otosclerotic stapes produce an exuberant, fibroblast like outgrowth mature otosclerotic lesions produce a less intense, more osteoblast like outgrowth. Concentrations of sodium fluoride up to 15 ppm have no deleterious effect on the cell growth or proliferation.

2 In organ culture sodium fluoride has a promoting effect on otosclerotic bone calcification.

3 In young rats, sodium fluoride definitely prevents experimental osteoporosis, whether this was induced by heparin or cortisone, as reported above or by fracture as reported in a previous paper.

4 When cert in phosphates ( $\text{Na}_2\text{HPO}_4$  and  $\text{KH}_2\text{PO}_4$ ) are associated with sodium fluoride a synergistic action produces a much better prevention of osteoporosis than either alone as seen by the experiment with cortisone.

5 From our experiment it appears that the best way to hinder and even prevent osteoporosis is to administer the sodium fluoride in small amounts for prolonged periods before heparin or cortisone intake or fracture, and then to give sodium fluoride with phosphates ( $\text{Na}_2\text{HPO}_4$  and  $\text{KH}_2\text{PO}_4$ ) afterwards.

6 What is essential is that the optimal dosage be found for each species, age and individual (as we have done for one strain of rat) to gain the favorable effect. Too high a concentration of sodium fluoride will have a deleterious effect on bone calcification. Often it is advisable to lengthen the time of treatment rather than strengthen the dosage.

7 These experimental findings strongly suggest that sodium fluoride along with phosphates might be useful in the treatment of patients with secondary osteoporosis, Paget disease and—perhaps—the otosclerotic stage of osteoporosis.

### ACKNOWLEDGMENTS

The authors gratefully acknowledge Miss Sheila Chilton for her assistance Mrs. Kathleen M. Rimoli for the histological work, and Miss James Alexander for the photography.

## RESUME

Chez le rat nouveau né le NaF en doses optimales favorise la calcification osseuse en entraînant à la fois une diminution de la résorption et une augmentation du dépôt calcique. D'autre part chez des rats de 6 à 8 semaines, le NaF prévient l'ostéoporose consécutive à la fracture surtout si on l'administre avant et après la fracture expérimentale et qu'on l'associe après fracture aux  $\text{Na}_2\text{HPO}_4$  et  $\text{KH}_2\text{PO}_4$ . Ces résultats furent obtenus grâce à une évaluation semi-quantitative au moyen de la tétracycline ainsi que par le microdosage du calcium.

## ZUSAMMENFASSUNG

Optimale Dosen von NaF fördern die Knochenkalzifikation in neugeborenen Ratten durch die Verminderung der Knochenresorption und durch Förderung der Kalziumablagerung. NaF verhindert ebenfalls durch Fraktur herbeigeführte Osteoporosis in 6-8 Wochen alten Ratten besonders wenn vor und nach experimenteller Fraktur verabreicht und nach Fraktur kombiniert mit  $\text{Na}_2\text{HPO}_4$  und  $\text{KH}_2\text{PO}_4$ . Beide Resultate wurden durch semiquantitative Auswertung von tetracykliner Markierung versus mikrochemische Kalziumbestimmung beobachtet.

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## DISCUSSION

*J. M. Tet:* Your experimental studies are very promising and support in some ways the use of  $\text{NaF}$  and phosphates, in osteoporosis, Paget Recklinghausen and osteogen is imperfect. We learn that it is necessary to use optimal doses. I want to ask the authors which are these optimal doses for osteoporosis and the other osteodystrophies.

*H. Kelemen:* Observation of rats with the inevitable nasal and paranasal suppurative condition undergoing similar medication might add results of practical interest.

*G. Shambaugh (Reply):* The exact etiology of localized osteoporosis of the labyrinth capsule (misnamed osteoporosis) is not known. The two diseases are not exactly associated, but there are similarities. Both are more frequent in females than in males, pregnancy and the menopause are predisposing factors, while heredity plays a part. The demonstration by Dr. Petrovic a beautifully controlled experiment that the generalized osteoporosis is caused by cortisone or heparin and the localized osteoporosis is the result of fracture can both be inhibited by sodium fluoride encourages us to hope that localized osteoporosis of the labyrinth capsule may be influenced in the same manner.

Our experiences up to date are little encouraging, but at the same time a little discouraging (laugh).

Experiment now under way in our laboratory indicate that the osteoporotic habit of diet of sodium fluoride is considerably strengthened by giving phosphates at the same time. This we are now starting to use in our patients with polyosteoritis demonstration of osteoporosis of the labyrinth capsule. I want in two years we will have sufficient data to know whether there is a real favorable effect on the clinical stage of sclerosis of the labyrinth capsule.

The dosage of these medication is as follows:

1. 10 mg. (one to 20 mg. per liter) twice daily.

2. 10 mg. (one to 20 mg. per liter) three times daily.

3. 10 mg. (one to 20 mg. per liter) three times daily.

4. 10 mg. (one to 20 mg. per liter) three times daily.

5. 10 mg. (one to 20 mg. per liter) three times daily.

6. 10 mg. (one to 20 mg. per liter) three times daily.

7. 10 mg. (one to 20 mg. per liter) three times daily.

8. 10 mg. (one to 20 mg. per liter) three times daily.

Method phase of remodelling process.

Lawson, N. G. H. M. R.

1. 10 mg. (one to 20 mg. per liter) three times daily.

*H. Petrus (Reply):* I wish to thank Mr. Kelemen for his very interesting report. Mr. Shambaugh has treated an unoperated *M. Tet* question. I just told that although we cannot extrapolate directly from multi-man studies of doses of sodium fluoride and phosphates, we have found that if the basis of comparison is the body weight, the rat requires more sodium fluoride for promotion of bone calcification than humans, but if the basis for comparison is the calcium intake, then the rat is in the same range of values, not forgetting individual differences of course.

## LIPOID MATERIALS IN THE COCHLEAR DUCT OF THE GUINEA PIG

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A cord of highly refrangible materials in the external spiral sulcus of the guinea pig's cochlear duct is described. It is present in all the cochlear turns except the basal turn. The materials are positive to Sudan III and Sudan Black, and are dissolved in alcohol and ether. With the same approach research is performed on other species: white mouse, rabbit, cat and man.

### INTRODUCTION

While performing dissections on the guinea pig's cochlea, we were surprised to find a material in the form of a cord, highly refrangible, floating easily in the watery medium and separating itself when the lamina was removed and placed in fresh material. The frequency of the findings completed us to investigate its localization and origin or try to identify it with some known elements of the cochlear duct.

### METHODOLOGY

Fifty guinea pigs were used, varying in weight from 70 to 600 g each. Sodium pentothal by the intra-abdominal procedure was used as an anesthetic. Dissection was performed with the retroauricle technique until the auditive bulla was localized. Using a dissection microscope, the bony lamina was separated from the cochlear turns. It was possible to keep the labyrinthine membranous part in place.

Using an 11 B.P. scalpel the modiolus was transversally cut at the level of each cochlear turn. The cuts were studied separately.

### FINDINGS

It was possible to observe in the angle formed by the basilar membrane and the spiral ligament a cord of granular aspect, highly refrangible and localized on the three superior turns, but in every case it was absent in the basal turn. The cord separates easily and tends to float. Its average thickness was 102  $\mu$  (microns) (Figs. 1 and 2).

This cord, observed *in vivo* or fixed in formaldehyde in phase contrast, is formed by numerous circular drops, the largest being 10 or 12  $\mu$ . The

FIG. 1. Guinea pig cochlea: Lipoid cord *in situ*

FIG. 2. Cord 1 gva lar perit, float g.

small ones are hardly visible with 1000 diameter. Under the drops, and difficult to see we found polygonal cells, placed next to each other very similar and with a small round and central nucleus (Fig. 3). The cytoplasm, with a slightly dense aspect, presents profuse chondriome and a rod-shaped chondriosome (Fig. 4). Accurate observation of these materials suggests, for the small drops, an intra-cellular localization, while for the larger drops, an extra-cellular localization.

The drops were quickly dissolved by alcohol and ether while observation was being carried out under the microscope. Nevertheless, no space appeared between the cells. The latter suggests that the larger drops were on top of the smaller ones, and not between them. To know more about its chemical composition, the following techniques were used: for general lipids, Sudan III and Sudan Black (MacManus & Mowry 1960) Smith's method (1908) modified by Cain (1947) showed us the neutral and acid lipids. Smith & Mair's technique, with Blue Nile, showed the phospholipids and the acid lipids. A method for identifying cholesterol was used, too, and hematoxylin-eosine as a routine method. The material was positive to all lipid techniques and always negative to cholesterol technique.

The liquid used to receive the material was Dulbecco's, but modified by us in its proportions of Na (Sodium) and K (Potassium). We increased the latter and decreased the former. This liquid was more tonic for the cells of the cochlear duct than any other saline solution previously recommended for diverse tissue. Nevertheless, since cellular swelling was observed, other liquids were used, too, such as Ringer's, Tyrode's and Gey's. Gey's was the best from the tonic point of view.

When, during dissection, the organ of Corti separates violently from the spiral ligament, usually the lipoid cord remains adhere to the external region of the organ of Corti. For this reason, we consider the cells that make up the lipoid cord to be cells of the external spiral sulcus. (Fig. 5)

The next step in our research was ear dissections on newly born guinea pigs. We found the lipoid cord in the same place and more or less with the



## LIPOID MATERIALS IN THE COCHLEAR DUCT OF THE GUINEA PIG

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A cord of highly refrangible materials in the external spiral sulcus of the guinea pigs cochlear duct is described. It is present in all the cochlea's turns except the basal turn. The materials are positive to Sudan III and Sudan Black and are dissolved in alcohol and ether. With the same approach research is performed on other species: white mouse, rabbit, cat and man.

### INTRODUCTION

While performing dissections on the guinea pig's cochlea, we were surprised to find a material in the form of a cord, highly refrangible, floating easily in the watery medium and separating itself when the lamina was removed and placed in fresh material. The frequency of the findings completed us to investigate its localization and origin, or try to identify it with some known elements of the cochlear duct.

### METHODOLOGY

Fifty guinea pigs were used, varying in weight from 70 to 800 g. each. Sodium pentothal by the intra-abdominal procedure was used as an anesthetic. Dissection was performed with the retroauricle technique until the auditive bulla was localized. Using a dissection microscope the bony lamina was separated from the cochlea's turns. It was possible to keep the labyrinth's membranous part in place.

Using an 11 B.P. scalpel the modiolus was transversally cut at the level of each cochlea's turn. The cuts were studied separately.

### FINDINGS

It was possible to observe in the angle formed by the basilar membrane and the spiral ligament a cord of granular aspect, highly refrangible and localized on the three superior turns, but in every case it was absent in the basal turn. The cord separates easily and tends to float. Its average thickness was  $102 \mu$  (microns) (Figs. 1 and 2).

This cord, observed *in vivo* or fixed in formaldehyde in phase contrast is formed by numerous circular "drops" the largest being 10 or 12. The

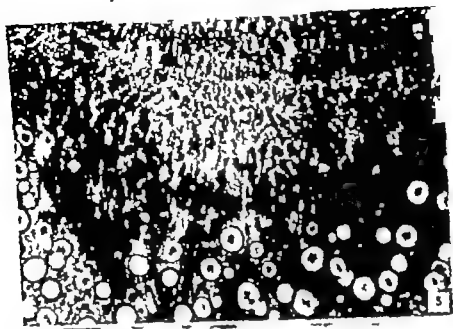


FIG. 5. Organ of Corti Cells of the external spiral locus.

FIG. 6. "Grumes" or lipid in the rat spiral ligament.

tainly were not as abundant as in the guinea pig. (Fig. 6.) In the rabbit and white mouse no lipid material was found in their cochlear ducts. In the human temporalis, no material similar to the guinea pig's lipid cord was identified. Using Sudan III and Sudan Black, fragments of the spiral ligament and the organ of Corti were tested. The results were negative.

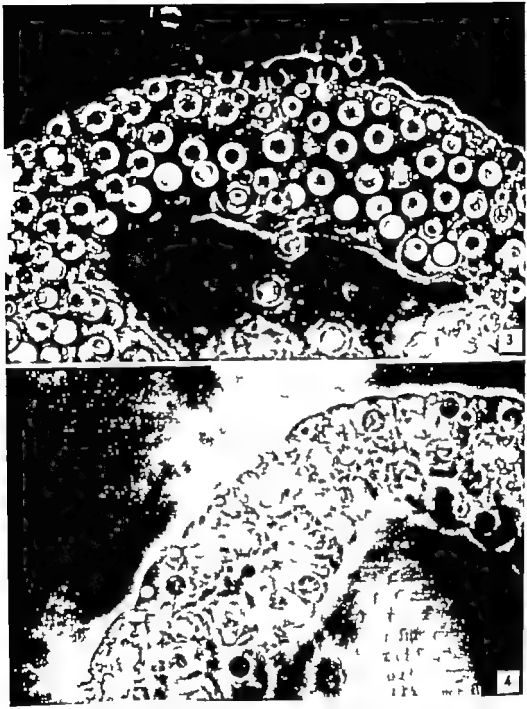


FIG 3 Pig n 1 II with th l round nd ce tral l  
FIG 4 C t p l m with h d r l m e, nd rod haped h d r l m

same dimensions as in the adult guinea pig. We continued the investigation on other species: cats, rabbits, white mice and some human temporals fixed in formaldehyde.

In the spiral ligament and more specifically in the cat's vascular stria, we found a few small grumes or clots, which were positive to Sudan III and Sudan Black, but the former did not have the shape of a drop and cer

4 In the cat a vascular strin were found small grumes or clots positive to Sudan III, but not a lipoid cord. In the rabbit white mouse and man, nothing similar was found.

5 It is suggested that the cells of the external spiral sulcus are the origin of the lipid drops.

## RESUME

Une corde à matériel lipofide est découverte dans le canal cochléaire du cobaye. Elle est formée par des substances grasses sur des cellules polygonales. Elles donnent une réaction positive Sudan III au Sudan noir et au Smith Mair et une réaction négative au cholestérol. Elle se dissout dans l'alcool et dans l'éther. Des études sont menées, dans le même but, sur des temporeux d'hommes, de chats et de rat blancs.

## ZUSAMMENFASSUNG

Eine Schnur gebildet aus Fettstoffen über polygonalen Zellen findet man in der Canalis cochlearis des Meerschweinchen. Die Reaktion auf Sudan III, schwarzem Sudan und Smith Mair ist positiv, die auf Cholesterin negativ und löst sich in Alkohol und Äther auf. Ausserdem werden Studien auf ähnlichen Zwecken an menschlichen Schläfenbeinen und Schläfenbeinen von Katzen und weissen Ratten erwähnt.

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## DISCUSSION

In the bibliography studied on the organ of Corti including old and new reports and with various techniques, no reference is found to these peculiar structures (Ballenger & Ballenger 1938 Beaunis & Bochart, 1873 Besold & Siebenmann, 1908) The only reference mentions Hensen's cells as having inclusions of lipid material (Maximov & Bloom 1952 Tonndorf 1962)

No doubt the main factor is that histological techniques use ether and alcohols for dehydration and embedding and these substances dissolve most of the lipid materials The possibility of confusing the lipid cord with some other structure of the organ of Corti such as, for instance the tectorial membrane that separates in the shape of a transparent ribbon was ruled out because both were easily obtained in the same samples

We think that the origin of this material might be the cells of the external portion of the basilar membrane, whose abundant chondriome is suggestive of high metabolic processes We can deduce, therefore, that we are not dealing with fatty tissue In the strict sense of the word, since in fatty tissue the intracellular fat increases with the gradual displacement of the cellular structures, pushing the cytoplasm towards the periphery of the cell and causing its death

In our material all the cells look alike and complete Their containing drops are very small giving the impression that the lipids soon become extra-cellular and coalesce to a certain limit, since drops or spaces too large were never found There is a remote possibility of the lipids being elaborated in another zone and clustered on the external spiral sulcus But up to now we have not seen them dispersed or in another region of the cochlear duct

In the same way we can discard the idea of lipophanerosis phenomena following cellular death, because in the guinea pig we have observed the lipid drops while the cells underneath are still alive

In human beings, we tried to confirm Del Bo's findings (1957) He insists that positive Sudan Black materials are present in the inner hair cells of the organ of Corti and in the vascular stria In spite of the modifications and variants applied to this technique, we obtained only negative results.

## CONCLUSIONS

1 A cord of lipid material in the external spiral sulcus of the guinea pig's cochlear duct is described

2 It is formed by drops of lipid materials on polygonal cells having abundant chondriome

3 The drops reacted positively to Sudan III Sudan Black and Smith & Mair's phospholipids, and negatively to cholesterol Alcohol and ether dissolve the drops

## STATISTICAL EVALUATION OF HEARING LOSSES IN MILITARY PILOTS

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Regression analysis is a valuable statistical technique for following the evolution of hearing loss over the course of time in acoustically traumatized subjects. On the basis of 786 audiograms of 673 Swiss military pilots, it was found that aging is the most significant factor influencing the threshold shift of the test group. In accordance with the relative acoustical characteristics of the flight noise patterns, propeller craft seem to cause more damage to hearing than do jets. By considering the standard deviation from the regression curves, single flyers may be selected out in order to get more information about the individual susceptibility to noise damage.

Many problems of noise-induced hearing loss have been solved during the last decade but, among others, an essential question has not yet been adequately answered. How much of an individual's threshold shift is really noise-induced and how much is due to aging?

The permanent threshold shift caused by the daily influence of industrial high-intensity noise seems to be established after 10-15 years of exposure (Glorig & Davis, 1961; Nixon & Glorig, 1961; Wagemann & Abihorn, 1963). A further diminution of hearing therefore would be the consequence of aging. A threshold shift due to noise and presbycusis are essentially different phenomena; they theoretically can be separated from each other by simple subtraction. Rosen's audiological and medical examinations of an African tribe threw new light on presbycusis (Rosen & Olin, 1965). He showed that in the phenomenon of presbycusis overall human aging plays a greater role than exposure to the noises of civilized life.

Most of the publications on noise-induced threshold shift deal with industrial and experimental noise sources of damaging intensity. Under these circumstances, individual sensitivity is of minor importance. Any individual exposed to such an intensity of noise over a certain period of time will be damaged sooner or later. However, susceptibility to noise varies among individuals and the susceptibility of a given individual probably fluctuates over time. From a prophylactic point of view people whose hearing loss develops under less traumatizing circumstances need our special attention. Preceding experiments (Beck & Beickert, 1958; Sato, 1958; v. Schultheiss,

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## DISCUSSION

G. Kelemen. It is encouraging to hear about investigations regarding the pathology of diseases of the lipoid group with their slowly accumulating clinical importance in otolaryngology.

TABLE 1 *Statistical evaluation of hearing loss in military pilots.*  
N = 673 pilots; 5786 audiograms.

Questionnaire
Pilot
Age
Noise protection during flight
Threshold shift for
500 cps, rt./lt. ear
1000 cps, rt./lt. ear
2000 cps, rt./lt. ear
4000 cps, rt./lt. ear
8000 cps, rt./lt. ear
Family history of hearing deficiency
History of illness
Non military noise exposure
Aircraft type
Propeller/jet helicopter
Flying time (time of exposure)
Hearing test
Audiometer types (1 2 3 4)

overlapping of the condition demonstrated in Fig 1 makes a statistical study necessary.

This report deals with the case histories of 673 pilots. These fliers had a total of 5786 bilateral threshold audiograms, which were computed in the Swiss Federal Statistical Bureau.

A purely statistical program was used to follow the evolution of the threshold shift of the whole group. The regression curves and their standard deviations were calculated. On the basis of these statistical findings the pilot whose hearing-loss exceeds the standard deviation will be selected for further study. Individual examinations of these pilots will be carried out. This study may throw light on the reason for their hearing-deficiencies, i.e. their sensitivity to noise damage. This paper deals with the purely statistical part of the program whereas the second project is going on at the moment.

#### METHOD

The age of the pilot, the threshold shift at various frequencies and dates, and the flying time are listed in the questionnaire example. Three types of aircraft (propeller, jet and helicopter) are considered (Table 1).

We are indebted to M. C. Inard for having collected the relevant data.



*Soundings reported during the study*

FIG 1

1961) have proved that, in the presence of subtoxic application of streptomycin or hypoxemia, a threshold shift can be produced by a noise which otherwise would be harmless.

This study attempts to approach the problem of these minor noise-induced threshold shifts by following the audiograms of a group of subjects over a certain period of time. A regression analysis permits a determination of the rate of diminution of the hearing in the group with aging and under the influence of certain traumatizing effects.

### MATERIAL

The effect of aging and exposure to flight noise in aircraft pilots was investigated. Swiss pilots are submitted to training flights every year. Auditory threshold tests are administered at regular intervals. Flying time is registered and the physical characteristics of the noise in the aircraft as well as the effect of noise protective measures are known (Fig 1). The

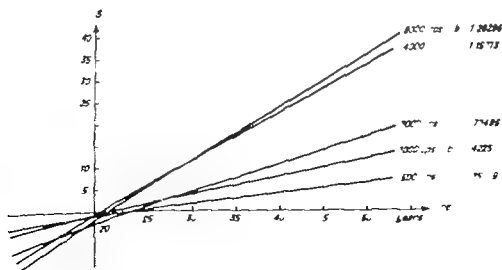
*Threshold shift of aircraft pilots (right ear)*

FIG 2

TABLE 2 Threshold shifts (dB) at 40 years of age

	freq.	500	1000	2000	3000	4000
Present study (flying staff)	Rt. ear	1.50	8.29	11.20	23.82	21.82
	Lt. ear	1.67	8.37	12.87	29.19	29.37
Other authors						
d. La Rue et al. (1953)		~7	~	~9	~12	~11
Glorig et al. (1951), Winneshko State Fair						
	Rt. ear	1.0	4.1	5.1	18.4	
	Lt. ear	1.6	4.8	6.2	21.6	
Asher Stand. Ass. (1934)					~12	
Corno (1950)					~17	
Glorig (1951)			~3	~2	~13	
Hinchcliff (1950)	17	17	2.6	8.3		3
A.E. (aging effect)						
Nixson & Glorig				1.36	7.6	

(c) Threshold shifts in the present study can be compared with the results of other authors. It is evident that in the present study there is a more remarkable threshold shift, especially in higher frequencies, than in other more or less selected groups (Table 2). This may be the consequence of other traumatizing agents, e.g. blast trauma, exposure to industrial noise etc.

## 2 The Relation of Threshold Shift to Flying Time

This correlation, too, can be demonstrated by regression curves. From these data the following conclusions can be drawn:

a) Aging and other eventual uncontrolled damaging factors have a greater influence on threshold shift than exposure to aircraft noise during flying time.

Threshold shift of air staff pilots (left ear)

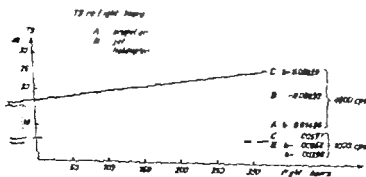


FIG. 5

Threshold shift of air craft pilots (left ear)

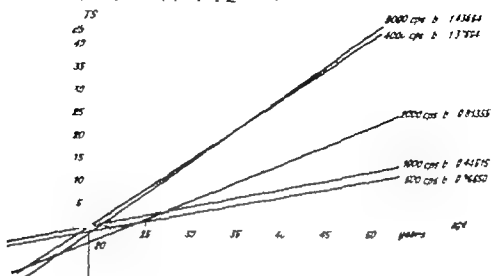


FIG 3

## RESULTS

## 1 The Dependence of the Threshold Shift on Age

(a) As expected the threshold shift increases with age. This fact can be readily demonstrated by regression curves (Figs 2 and 3). The frequencies of 4000 cps [and 8000 cps] are more affected than the lower frequencies.

(b) As mentioned by other authors, the left ear shows an auditory threshold higher than the right ear (Glorig *et al.*, 1957; Iicler & Reger 1958; Opplinger *et al.* 1960) (Fig 4).

Threshold shift of air craft pilots (right ear)

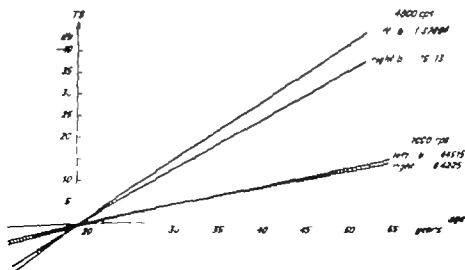


FIG 4

TABLE 2 Threshold shifts (dB) at 10 years of age

	cps	500	1000	2000	4000	8000
Present study	RL ear	1.50	8.29	11.20	33.82	21.62
(Flying staff)	LL ear	1.67	8.37	12.87	28.19	23.37
Other authors						
de Roo (1933)		~7	~7	~9	~13	~14
Glorig <i>et al.</i> (1931), Wisconsin State Fair						
	RL ear	1.0	4.1	5.1	18.8	
	LL ear	1.6	4.6	6.2	21.5	
Amer. Seand. Ass. (1934)					~12	
Cornu (1939)					~17	
Glorig (1961)			~2	~2	~12	
Hartshill (1959)		1.7	1.7	2.3	5.3	3
AE (aging effect)						
Nixon & Glorig				1.38	7.6	

(c) Threshold shifts in the present study can be compared with the results of other authors. It is evident that in the present study there is a more remarkable threshold shift, especially in higher frequencies, than in other more or less selected groups (Table 2). This may be the consequence of other traumatizing agents, e.g. blast trauma exposure to industrial noise etc.

## 2. The Relation of Threshold Shift to Flying Time

This correlation, too, can be demonstrated by regression curves. From these data the following conclusions can be drawn:

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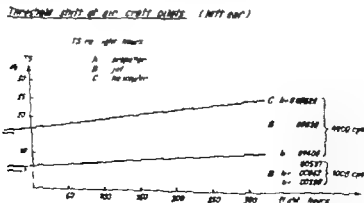


FIG. 5.

## Threshold shift of air craft pilots (right ear)

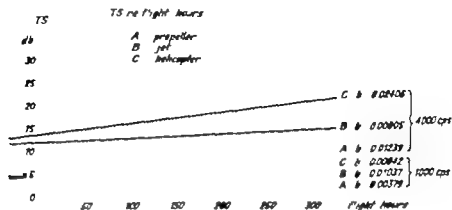


FIG. 6

(b) The effect of the noise of helicopters on hearing is more important than that of propeller craft and jets. There is only a slight difference between the latter two, the jets being less traumatizing (Figs 5 and 6)

(c) The helmet worn in jets seems to be a valuable protector against traumatizing noise

TABLE 3 *Multi regression*  
 $N = 5780$

cps	dB/year ( $p < 0.001$ )	Threshold shift
		At 31 years (mean) 789,041 hr propeller 229,300 h jet 14,221 hr helicopter
500		
Rt	-0.481	-2.423
Lt	-0.462	-2.462
1000		
Rt	-0.4408	-1.793
Lt	-0.4734	-1.682
2000		
Rt	0.5932	3.192
Lt	0.032	0.121
4000		
Rt	-0.9451	-14.221
Lt	-1.2470	-17.060
8000		
Rt	1.1834	-13.021
Lt	-1.4620	-16.460

### 3. Multiple Regression Analysis

The evolution of threshold shift in the present study can be determined by a multiple regression analysis, which considers both aging and noise effect simultaneously. This three-dimensional function cannot be demonstrated by two-dimensional curves. For this reason the result of this analysis is shown in the following table which demonstrates the progression of threshold shift in the study group. The mean value for the whole group shows the rate of progression per year and the hearing loss for a calculated mean age and a calculated mean flying time (Table 3).

### CONCLUSIONS

Statistical evaluations of quantitative medical tests, e.g. the threshold shift in audiometry unquestionably face limitations. Well known facts may be confirmed and new hypotheses may be generated. Simple and multiple regression analysis make it possible to study over a long period the effect of certain damaging factors on permanent threshold shift.

Presbycusis is a clearly defined process with unquestionable audiological properties (Glorig & Davis, 1961). These are known to be very complex. On the other hand, many people undergo the influence of civil, military and occupational noise which acts as a subliminary potential or effective damaging agent. Its consequence, the so-called "sociocusis" (Glorig & Nixon, 1960) is a threshold shift practically inseparable from the aging process. By considering all the measurable factors which may influence hearing capacity it is possible to determine their real damaging effect. Individuals who fall outside the standard deviation of threshold shift might sooner or later be handicapped by a severe hearing loss. They can be examined by individual tests and eventually extricated from their damaging environment before permanent hearing loss is established.

### RÉSUMÉ

Vous analysez statistiquement 786 audiogrammes chez 673 pilotes militaires, vous pouvez la méthode dite de *régression multiple*. Ainsi les relations entre le seuil auditif et l'âge des pilotes d'un part et le temps d'exposition au bruit d'autre part ont été déterminés. Sur la base d'écart-type des valeurs de progression, les pilotes menacés d'une diminution d'audition peuvent être détectés et soumis à un examen médical approprié.

### ZUSAMMENFASSUNG

Die vorliegende Arbeit stützt sich auf insgesamt 778 Schwellenaudiogramme 673 Schweizer Militärpiloten. Mit einfachen und multiplen Regressionsana-

hasen wird die Progredienz der Hörschwellenverschleibungen im Verlauf der Zeit statistisch untersucht. Es zeigt sich eine eindeutige Altersabhängigkeit der Regressionskurven. Daneben lässt sich aber auch eine Gehörschädigung in Abhängigkeit von der Dauer der Belastung mit Fluglärm nachweisen. In Übereinstimmung mit den durchgeführten Analysen ist der Fluglärm der Kolbenmaschinen schädlicher als derjenige der Düsenjäger. Aufgrund der berechneten Streuung der Regressionswerte können vorzeitig geschädigte Piloten erfasst und einer individuellen medizinischen Untersuchung zugeführt werden.

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## DISCUSSION

- M. Portmann: Tous les auteurs remarquent une différence de traumatisme entre le côté droit et le côté gauche.  
Est-ce le fait des conditions de pilotage?  
Est-ce une sensibilité plus grande du côté gauche?

Je pense plutôt à cette deuxième hypothèse. Dans le cas du *Mr v. Schulthess*, a-t-il étudié statistiquement le trauma sonore en relation avec la latéralisation (gauche et droite)?

*Dr Davis* The opportunity for careful longitudinal studies of this sort is rare and should be exploited fully. How long does each man remain in the study? Do the individual remain in the same relation (percentage) to the group from test to test? What is the base for the "threshold shift"? Is it the man's first audiogram or is it really the "hearing level" or the iso audiometric threshold?

It is good to observe that the threshold shifts are not very large. I would not expect any of these subjects to complain of impaired hearing. Did they complain?

*G. Shambaugh* We have obtained polytomic studies of the cochlear capsule in cases of presbycusis with greater-than-expected loss for the age group. A certain number of these prove to have cochlear otosclerosis, rather than presbycusis, causing their histologic loss. The racial incidence in presbycusis noted by Rosen and mentioned by von Schulthess, where the African Malays and the Indians have less presbycusis than we usually see might be due to the relative rarity of otosclerosis in negroes.

I was impressed by the greater loss in the left ear noted by von Schulthess. Could this be due to the target practice required of Swiss military pilots, where the left ear of right-handed persons suffers more noise damage?

*A. Platonov* J'ai remarqué de façon constante, l'anomalie signalée par *M. v. Schulthess* chez les pilotes d'Air France. Je ne pense pas, ainsi que l'a suggéré le *Dr Portmann*, que la cause de cette anomalie du type droitier ou gaucher mais plus simplement un problème purement physique de situation même du pilote placé sur la gauche de l'appareil et de ce fait présentant un trauma plus marqué du côté gauche.

*Dr Schulthess (Reply)* *Dr Portmann* We do not know the reason for the differences in the threshold shift at 4000 cps between the right and the left ear. They cannot be the consequence of noise-influence as Glorig in his Wisconsin State Fair survey 1937 tested an unselected group of the population and got the same results. There may be a correlation with right and left-handedness, which has not been proved yet.

*Dr Davis* The single subject included in the study for different periods of time which depends on the age when it enters military service. Accordingly the individual exposure period is different. The different kinds of aircraft noise varies. These facts make it necessary to approach the problem by the proposed statistical method.

Our "threshold shift" refers to the audiometric zero level which was suggested according to international convention during the period of the study. This fact is taken into consideration as mentioned in Slide 1. We agree with the discoverer that the hearing loss due to flight noise is not very pronounced in our graph. However we wish to emphasize the fact that in the curves of Figs. 7 and 8 we are dealing with mean values. There are single subjects whose threshold-shift is far outside of the standard deviation and we think that clinical examination of these may bring us closer to the problem of sensitivity to hearing-damage.



## TOE PITCH INTELLIGIBILITY HEARING ADAPTATION AND FATIGUE

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Ten of 70 tested musicians and members of choirs were able to discriminate without error and remember different tone pitch and loudness thresholds. Peristimulatory fatigue for the tones C<sub>2</sub>, C<sub>4</sub>, C<sub>5</sub> and C<sub>6</sub> at intensities of 50-80 dB was evident. Its degree was determined by the loudness balance of 35 dB in approx 2-3 min. Adaptation took place during 5-10 sec depending on the sensitivity of the tested person.

The ability to keep in mind correctly and precisely the loudness thresholds of different high and tone pitch perceptions does not coincide with a gifted memory for melodies and rhythms. The first mentioned musical ability is called "absolute tone pitch intelligibility" and is a faculty of a small number of musicians who can easily remember melodies, their rhythmical sequences, musical intervals and, of course the frequency and tonality of their different components. A musical talent means, therefore a special capacity in the rapid association of tones and melodies, which leaves in the memory more or less precise "acoustical images".

The investigations of G. Hensen, in year 1878 proved that the ear is very sensitive to tones of 1000 cps (C<sub>5</sub>), the difference in vibrations of this "optimum audible" amounts to 0.4-1/sec while in tones over 3000 cps (C<sub>6</sub>, A<sub>6</sub> and G<sub>6</sub>) a difference of 100 vibrations can be seen. In two simultaneous resounding tuning forks the smallest interval which can be detected by the ear is to be found between 500-501 vibrations/sec which is equal to 1/60th of a half tone. The ability to discriminate fractions of different tones and musical accords using various instruments was called by Jentsch the "absolute connoisseurship of tones". It must be stated that this kind of tone intelligibility does not make indispensable any musical ability in which there is adequate skill in the discrimination of the frequency and tonality of sounds and voices beside their rhythmical perseverance and, additionally a special capacity in the memory for melodies. As for the latter ability a great deal of observation has proved that it is easier to fix in the memory the sequences of tones than their pitch level.

I had an opportunity to perform audiometrical examinations in 10 musical ensembles, i.e. 8 pianists, 4 violinists, 1 composer, 24 advanced students of music and 34 members of choirs (aged 21-40 years). These examinations proved that only 10 i.e. 4 of this group were able to remember the supraliminal loudness of the audiometric tones (Amplivox). In this test the

scale used was from  $C_{125}$  to  $C_{2000}$  cps with an intensity of 35-60 dB. At intervals of 8-15 min the same scale was repeated and the examinee asked if the intensity of the given tone corresponded with that of the loudness threshold. After an interval of 15 min this scale was used in the reverse direction, i.e. from  $C_{2000}$  cps and 100 dB to  $C_{125}$  cps and 25 dB intensity. It must be said that on both occasions the examinees, 3 pianists (aged 27-31 and 40 years), 4 violinists (30, 32, 34 and 38) and 3 qualified students of a musical academy (21, 23 and 24) were able to discriminate precisely and remember the different tone pitch and loudness thresholds, while the other group of 60 students defined the various tones of scale too high, at an intensity of 25 dB, and then too low when tested in the reverse direction of the scale.

The errors in the loudness discrimination fluctuate on average between 10-20 dB. The 10 students with the gift of absolute connoisseurship of tones were able to discriminate and remember the different tone pitch. With regard to this question, it must be mentioned that in order to get the perstimulatory fatigue produced by a stimulus with tones of  $C_{2000}$ ,  $C_{1000}$ ,  $C_{500}$  and  $C_{250}$ , I strengthened successively its intensity from 50 to 110 dB for one min. The time of recovery and restoration to normal conditions, following fatigue was marked by an increase in a number of decibels for every 10 sec after cessation of the fatiguing tone. The individual deviation of behaviour at the critical point of the stimulus intensity must be considered. In a great number of the cases examined, of 21, 27, 28, 24 and 31 years, this point was calculated to be between 90 and 100 dB and only in 3 violinists of 32, 34 and 38 did it appear just at the intensity of 80 dB.

In the first series of examined cases the magnitude of the fatigue was of a lesser degree below 90 dB. In the second series it was just below 80 dB. On the other hand, above these critical points the perstimulatory fatigue appeared at once with considerable intensity. This kind of aural fatigue must be differentiated from deafness caused by strong acoustic stimulus (stimulation deafness) as a pathological symptom, due to irritation of the cochlea by over intense tones, which is quite different from physiological fatigue. The critical point of which is below the threshold of pain, with a tone intensity of 120 dB. It happens, however that this unusual symptom reveals itself just after less to 20 min, despite the discontinuance of the above mentioned irritation or it persists for a shorter or longer time as a post-traumatic sequelae of this hearing disorder (a disturbed chemical composition and bioelectrical processes within the perilymph, the basilar and tectorial membranes (v. Békésy 1960, Kylin 1960)).

The diagrammatic curves of the tested perstimulatory fatigue in the 10 students with absolute connoisseurship of tones show that 3 of them were more sensitive to aural fatigue than the other 7; however a logarithmic relation between the time of duration of the short acoustic stimulus and aural fatigue was invariable in all (Fig. 1 and 2). In contradiction to the high tones of  $C_{2000}$  to  $C_{500}$  cps, the lower tones produce a limited

variety of fatigue which is not constant with the stimulus intensity of the testing tone this particularly justifies the concept of a dual mechanism of acoustical sensations, i.e. the high tones are perceived by that part of the cochlea which is exposed to the static variations of pressure and the middle-low tones which accomplishes because of the varying phasic changes in the endolymph towards helicotrema as well

Perstimulatory fatigue in the 10 students during the masking of the contralateral ear did not depend on the stimulus intensity but rather on the response of the nerve elements of the inner ear (Stevens & Davis, 1938; Hood, 1955). Using an appropriate arrangement to stimulate both ears by tones of the same frequency i.e. 500–1000 cps and 80 dB intensity varying at the tested ear only (but the opposite ear was under the influence of the loudness of the constant tone). The type and degree of auditory fatigue was determined by the intensity of the variable tones (loudness balance) which in the tested cases reached their maximum of 35 dB in about 3 min remaining at an invariable level.

It is notable that in contradistinction to poststimulatory fatigue perstimulatory fatigue resembles the recruitment phenomenon. The state of recovery of perstimulatory fatigue takes place quickly during the first 5–10 sec, then decreases slowly until its maximum is reached in 50–60 sec. This particularly justifies the assumption of Matthews that in such cases there exists a regeneration of the neural elements within the peripheral part of the auditory apparatus. Even the relation of the above mentioned process to the intensity of the auditory stimuli indicates that the perstimulatory fatigue increases with the stimulus intensity while individual sensitivity to the fatiguing tone or other conditional psychical factors must be taken into consideration.

Working from the investigations of Ruben & Sekula (1961), Brunetti (1961) and Palva (1954) I was able to show that the perstimulatory fatigue in the tested cases was considerably shortened by using simultaneously the visual, olfactory, gustatory or thermal (skin) stimuli, which in turn indicates the dependance of the fatigue in question on the central nervous system in particular the reticular formation (Maspétiol *et al.* 1961). As for the poststimulatory fatigue there is a remarkable increase when the stimulus intensity crosses a certain point of the critical level. It is interesting that in all 10 students endowed with absolute tone pitch intelligibility perstimulatory fatigue appeared steady after 2–3 min at the intensity of 80–90 dB confirming its dependence on the magnitude of the receptor area within the cochlea in particular on the number of external and internal hair cells following fatigue. This kind of aural fatigue passes our comprehension on the physiological activity of the inner ear and reticular formation receptors and now it must be considered from the point of view of the law governing neural activity (Stevens & Davis, 1938).

Alternate balance using stimuli of constant intensity and duration from 1–5 min to the tested ear then a tone of the same frequency and varying

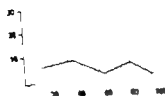


FIG. 1

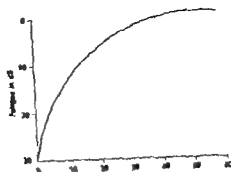


FIG. 2

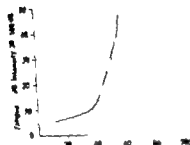


FIG. 3

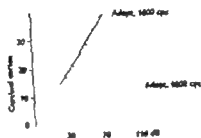


FIG. 4

FIG. 4 A comparison between the slow cortical potential moving from the electroencephalogram and the coherenceencephalogram.

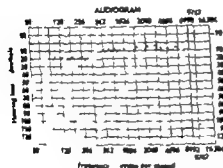


FIG. 5

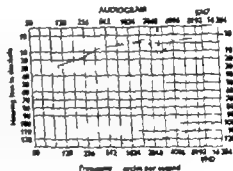


FIG. 6

intensity the contralateral ear supplied the peristimulatory fatigue of the student with such particular that the fatigued ear during acoustical stimulation persisted for a time despite cessation of the fatiguing tone of 1000 cps. Even when this acoustic stimulus was applied again after a lapse of 10-60 sec and its previous sudden interruption, an unfatigued level appeared at first followed by rapid relapse to the fatigue level, which could be seen clearly in these tested cases. The state of recovery appeared most



F 7

clearly during the first ten seconds, reaching its peak point after 60 sec similar to the recovery process of adaptation (Diagram (Fig 3)) Hearing adaptation and perstimulatory aural fatigue have quite different meanings, the former indicating one physiological process of recovery from the disturbed condition of the latter (M Portmann & Cl Portmann, 1954 Lüscher 1952 Hahn 1962 Szpunar 1953) Experiments on animals revealed that it could be stated that the short adaptation of the Corti organ, contrary to the longer one taken from the auditory cortex. It means the difference between the peripheral and central adaptation. It could also be proved that one restraining influence on the adaptation phenomenon within the Corti organ from the auditory cortex and the central auditory pathways as well as through the efferent fibres. The adaptation test in normal and inner ear disturbances, using the computer technical mediator revealed one characteristic difference between the slow acoustical cortical potentials, getting from the audioencephalogram and the cochlear one (Fig 4)

In order to complete the total audiological examination and physiological factors involved in tone and loudness perception by these musicians endowed with absolute tone pitch intelligibility I used additionally three hearing tests Jerger's "Sisi" Feldmann's and Fowler's tests. The first is a simplified method to delineate the difference in tone intensity by stimulation of the ear with lower tones and simultaneously a constant loudness of equal intensity of 20-40 dB in the opposite ear. The tested person perceives the tones 250-8000 cps at an intensity of 20 dB during two min at which point this intensity is augmented every 3 sec with 1 dB i.e. we can note 20

elevations in the audiogram during two min as an equivalent of 100% of the normal "Sisi" test (Fig. 5)

In the modified dichotic Feldmann's test the threshold curve and loudness control equality is denoted at first, then a 3000 cps tone of 80 dB is included for 4 min while the threshold point of the loudness is established. Performing the last survey one min after switching off the loudness control we get an adaptogram in which the  $a$  squared area indicates the efficiency of the organ of Corti and the  $b$  are the efficiency of the ganglion or cochlear nerve. It must be mentioned that the normal values for the  $a$  area are calculated to 300-500 and that of the  $b$  area to 1000-1500 mm<sup>2</sup>.

Fowler's test, modified by Lüscher-Zwischöckl, was performed too. Using certain modifications of the first two tests on the whole margin of its scale and intensity of 20-30 dB I achieved in the 24 advanced students of music auditory threshold tracings which become narrower i.e. from 12-0.3 dB, not only during the increase in intensity but also in frequency up from 1250 cps. The normal threshold for intensities 15-20 dB was calculated as 1.5-4 dB and for 30 dB as 1-3 dB.

Having performed Fowler's modified test, I was convinced that the threshold values are higher than those obtained by the authors of the original test in question (Fig. 6). The threshold differentiation of loudness by the 10 students endowed with absolute tone pitch intelligibility was generally lower corresponding more or less to the details given by Knudsen & Jones, 1933; Shennore 1890 and Tieplow quoted by Slezurek, 1966. Even the ability to keep in mind the loudness thresholds of different high tone and supraliminal pitch perceptions showed a certain deviation with a tendency to drop downwards. Regarding the bone conduction test in the 10 students I stated that the crossperception of the tones  $C_1$  and  $C_2$  was evident at a weak intensity of 4-7 dB when the receptor was placed on the parietal region of the head but it was much clearer especially at lower frequencies, and at the same intensity when Jendrassik's manoeuvre (Tyll) was applied, i.e. a strong compression of the examiner's hand by the examinee (Fig. 7). This manoeuvre consists in the mobilisation of the  $a$  and fibres of the component of the motor nerves, while the receptors of Golgi-Mazzoni-like type nerve endings lying around the muscle fibres and their tendinous lengthenings of the skeletal muscles, including tensor tympani andapedius, are set in action.

#### RESUME

La perception des sons, l'adaptation et la fatigue ont été examinées chez 20 musiciens. 10 ont pu discerner et se rappeler sans aucune erreur les différentes hauteurs des sons et les résultats d'addition, la fatigue pour les sons  $C_3$ ,  $C_4$ ,  $C_5$ ,  $C_6$ , pour l'intensité de 50-80 dB était évidente. L'adaptation se faisait pendant 3-10 sec. Il dépendait de la sensibilité individuelle. La fatigue a été mesurée par l'épreuve de Fowler (33 dB en 2-3 min).



FIG 7

clearly during the first ten seconds reaching its peak point after 60 sec, similar to the recovery process of adaptation (Diagram (Fig 3)) Hearing adaptation and perstimulatory aural fatigue have quite different meanings, the former indicating one physiological process of recovery from the disturbed condition of the latter (M Portmann & Cl Portmann, 1954 Lüscher 1952 Hahn 1962 Szpunar 1953) Experiments on animals revealed that it could be stated that the short adaptation of the Corti organ, contrary to the longer one taken from the auditory cortex. It means the difference between the peripheral and central adaptation. It could also be proved that one restraining influence on the adaptation phenomenon within the Corti organ from the auditory cortex and the central auditory pathways as well as through the efferent fibres. The adaptation test in normal and inner ear disturbances, using the computer technical mediator revealed one characteristic difference between the slow acoustical cortical potentials, getting from the audioencephalogram and the cochlear one (Fig 4)

In order to complete the total audiological examination and physiological factors involved in tone and loudness perception by these musicians endowed with absolute tone pitch intelligibility I used additionally three hearing tests: Jerger's, Sisi's, Feldmann's and Fowler's tests. The first is a simplified method to delineate the difference in tone intensity by stimulation of the ear with lower tones and simultaneously a constant loudness of equal intensity of 20-40 dB in the opposite ear. The tested person perceives the tones 200-8000 cps at an intensity of 20 dB during two min at which point this intensity is augmented every 3 sec with 1 dB, i.e. we can note 20

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## ZUSAMMENFASSUNG

Zehn von 70 untersuchten Musikern und Mitgliedern von Gesangsvereinen waren im Stande verschiedenartige hohe Grundtöne und lärmartige Schwellen fehlerfrei zu unterscheiden und sich an sie zu erinnern. Hörermüdung für die Töne  $C_2$ ,  $C_4$ ,  $C_5$ ,  $C_6$  in der Stärke von 50–80 dB war deutlich, deren Grad durch Lärmschwellen-Ausgleich von 33 dB in ungefähr 2–3 Min. bestimmt wurde. Adaptation fand während 5–10 sec statt und war abhängig von der Empfindlichkeit des Untersuchten.

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ÉTUDE D'UNE MÉTHODE D'EXPLORATIONS FONCTIONNELLES  
DES SYNDROMES VESTIBULAIRES PAR L'ASSOCIATION DE  
L'ELECTRONYSTAGMOGRAPHIE, DE  
L'ELECTROMYOGRAPHIE ET DE LA  
STATOKINÉSIMÉTRIE

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Notre travail a été entrepris dans le but d'adapter un nouvel appareil d'enregistrement le statokinésimètre aux explorations fonctionnelles otoneurologiques. Cette étude a été réalisée sur 21 sujets normaux et pathologiques et nous a finalement permis de préciser les grandes lignes d'une méthode dont le principe est d'associer trois techniques d'enregistrement pour connaître d'une façon plus détaillée la réponse à une stimulation vestibulaire calorique.

TECHNIQUES D'ENREGISTREMENT

*Statokinésimètre*

Cet appareil permet d'étudier les déplacements, dans les quatre directions cardinales, du centre de gravité d'un sujet en station verticale.

L'appareil comprend une bascule comportant un système de capteurs de pression sur lequel se place le sujet en position de recherche du signe de Romberg, un système d'enregistrement traduisant les variations de pression dues aux déviations captées par la bascule.

Pour les épreuves que nous avons réalisées, l'appareil original a été modifié de telle sorte que l'enregistrement des déplacements du centre de gravité soit fait en fonction du temps sur un inscripteur à plume Visiograph Alvar, deux lignes étant réservées : l'une aux déviations antéro-postérieures, l'autre aux déviations latérales.

*Electronystagmographie*

Des électrodes d'argent chloruré sont mises en place selon la façon habituelle pour l'étude des déviations horizontale et verticale. L'enregistrement est fait sur deux des quatre axes EEG du Visiograph.

*Electromyographie*

Des électrodes d'argent chloruré de surface sont mises en place sur la jambe gauche. Une paire d'électrodes antérieures au niveau du muscle jambier antérieur, une paire d'électrodes postérieures au niveau du triceps sural, une électrode reliée à la terre est placée sur la jambe droite. Les registres sont soit sur les deux autres voies EEG du Visiograph.

Au total on dispose de 3 lignes d'enregistrement. Electromyographie postérieure et antérieure, électrooculographie horizontale et verticale, déviations antéro-postérieure et latérale.

## PROTOCOLE D'EXAMEN

Après les réglages et calibrations des 6 voies d'enregistrement, le sujet est prié de monter sur la bascule ou il se tient debout, les pieds nus, dans la position du garde à vous. Plusieurs 'preuves sont alors faites.

— On étudie les déplacements volontaires du sujet dans les 4 directions et l'activité électromyographique concomitante.

— un enregistrement est ensuite fait en demandant au sujet de regarder dans l'obscurité une barre verticale phosphorescente placée à 3 mètres devant lui pendant 30 secondes.

puis on effectue un enregistrement de même durée et dans la même position, mais les yeux fermés.

Ces épreuves préliminaires étant terminées, (et après avoir constaté que le sujet était normal) sa tête est inclinée d'environ 60° en arrière les yeux étant fermés. Après que l'on ait noté la position du centre de gravité sur l'enregistreur un réglage est effectué pour placer les plumes en position médiane.

## STIMULATION

La stimulation de l'appareil vestibulaire est faite après vérification du conduit auditif externe par irrigation calorifique à la seringue avec de l'eau à 21°. Plusieurs doses sont utilisées pour chaque oreille : 2 cc et 4 cc, avec un débit de 1 cc par seconde. Après les irrigations, l'enregistrement est poursuivi pendant 130 à 230 secondes suivant l'intensité de la réponse. Ensuite le sujet se repose en position assise. La constatation de la disparition du nystagme dans la position de stimulation est effectué avant chaque nouvelle irrigation.

## RESULTATS

*Déviations*

Les déviations se font toujours en avant et du côté de l'oreille irriguée.

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ÉTUDE D'UNE MÉTHODE D'EXPLORATIONS FONCTIONNELLES  
DES SYNDROMES VESTIBULAIRES PAR L'ASSOCIATION DE  
L'ELECTRONYSTAGMOGRAPHIE, DE  
L'ELECTROMYOGRAPHIE ET DE LA  
STATOKINÉSIMÉTRIE

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Notre travail a été entrepris dans le but d'adapter un nouvel appareil d'enregistrement le statokinésimètre aux explorations fonctionnelles otoneurologiques. Cette étude a été réalisée sur 71 sujets normaux et pathologiques et nous a finalement permis de préciser les grandes lignes d'une méthode dont le principe est d'associer trois techniques d'enregistrement pour connaître d'une façon plus détaillée la réponse à une stimulation vestibulaire calorique.

TECHNIQUES D'ENREGISTREMENT

*Statokinésimètre*

Cet appareil permet d'étudier les déplacements, dans les quatre directions cardinales, du centre de gravité d'un sujet en station verticale.

L'appareil comprend : une bascule comportant un système de capteurs de pression sur lequel se place le sujet en position de recherche du signe de Romberg ; un système d'enregistrement traduisant les variations de pression dues aux déviations captées par la bascule.

Pour les épreuves que nous avons réalisées, l'appareil original a été modifié de telle sorte que l'enregistrement des déplacements du centre de gravité soit fait en fonction du temps sur un inscripteur à plume Visiograph Alvar deux lignes étant réservées : l'une aux déviations antéro-postérieures, l'autre aux déviations latérales.

*Electronystagmographie*

Des électrodes d'argent chloruré sont mises en place selon la façon habituelle pour l'étude des déviations horizontale et verticale. L'enregistrement est fait sur deux des quatre voies FEC du Visiograph.

### *Electromyographie*

Des électrodes d'argent chloruré de surface sont mises en place sur la jambe gauche. Une paire d'électrodes antérieures au niveau du muscle jambier antérieur, une paire d'électrodes postérieures au niveau du triceps sural, une électrode reliée à la terre est placée sur la jambe droite. L'enregistrement est fait sur les deux autres voies EEG du Visiograph.

Au total on dispose de 6 lignes d'enregistrement : électromyographie postérieure et antérieure, électrocnélagmographie horizontale et verticale, déviations antéro-postérieure et latérale.

### PROTOCOLE D'EXAMEN

Après les réglages et calibrations des 6 voies d'enregistrement, le sujet est prié de monter sur la bascule où il se tient debout, les pieds nus, dans la position du garde à vous. Plusieurs épreuves sont alors faites :

— On étudie les déplacements volontaires du sujet dans les 4 directions et l'activité électromyographique concomitante.

— un enregistrement est ensuite fait en demandant au sujet de regarder dans l'obscurité une barre verticale phosphorescente placée à 3 mètres devant lui, pendant 30 secondes.

— puis on effectue un enregistrement de même durée, et dans la même position, mais les yeux fermés.

Ces épreuves préliminaires étant terminées, (et après avoir constaté que le sujet était normal) sa tête est inclinée d'environ 60° en arrière, les yeux étant fermés. Après quoi on a pu noter la position du centre de gravité sur l'enregistreur un réglage est effectué pour placer les plumes en position médiane.

### STIMULATION

La stimulation de l'appareil vestibulaire est faite après vérification du conduit auditif externe par irrigation calorifique à la seringue, avec de l'eau à 24°. Plus faibles doses sont utilisées pour chaque oreille : 2 cc et 4 cc, avec un débit de 1 cc par seconde. Après les irrigations, l'enregistrement est poursuivi pendant 1'30" à 2'30" suivant l'intensité de la réponse. Ensuite le sujet se repose en position assise. Un contrôle de la disparition du nystagmus dans la position d'illumination est effectué avant chaque nouvelle irrigation.

### RÉSULTATS

#### *Déviations*

Les déviations se font toujours en avant et du côté de l'oreille irriguée.

Les déviations latérales sont les plus précoces, elles apparaissent au bout d'un temps moyen de (2 cc) 9 sec. (4 cc) 7 sec.

— La déviation antérieure lui succède elle apparaît en moyenne au bout de (2 cc) 11 sec, (4 cc) 10 sec.

Leur durée est au minimum de

— latérale (2 cc) 55 sec, (4 cc) 91 sec

— antérieure (2 cc) 66 sec, (4 cc) 115 sec

En réalité les déviations se prolongent le plus souvent au-delà de la fin de l'enregistrement

Il semble néanmoins que les déviations latérales soient légèrement plus courtes que les déviations antérieures

### *Electromyographie*

a) Au repos le triceps sural est en activité permanente. Cette activité paraît être en relation avec la déviation postérieure du centre de gravité rencontrée normalement chez tous les sujets.

— Par contre le jambier antérieur est dans la plupart des cas silencieux

b) Lorsque l'on demande au sujet de se déplacer volontairement dans le sens antéro-postérieur on constate que

— le déplacement du centre de gravité en avant s'accompagne d'une importante activité isolée du triceps sural,

— alors que le déplacement en arrière s'accompagne d'une importante activité isolée du jambier antérieur

Ces activités suggèrent qu'au cours des déplacements du centre de gravité et pourvu que la plante des pieds reste en contact avec la bascule, ces deux muscles s'opposent à des mouvements de grande amplitude

c) Après la stimulation calorique on constate des résultats variables

— soit une absence de modification de l'activité de repos,

— soit un renforcement isolé de l'activité du triceps sural qui apparaît en moyenne après (2 cc) 17 sec, (4 cc) 13 sec lorsque le déplacement antérieur atteint sa valeur maximum et persiste jusqu'à ce que le sujet ait tendance à revenir à la position d'équilibre normal

Chez certains sujets le jambier antérieur est le siège d'une activité modérée apparaissant après (2 cc) 20 sec, (4 cc) 9 sec, donc approximativement contemporaine de l'activité du muscle postérieur et de la déviation antérieure maximum

Dans certains cas cependant cette activité est très précoce et paraît due à des oscillations vers l'arrière que l'on constate parfois au début des réponses

Il est apparu d'ailleurs que l'activité du jambier antérieur dure moins longtemps que la déviation du centre de gravité

De ces enregistrements il ressort que l'activité de ces muscles a en général un rôle de frein contrôlant les déplacements du centre de gravité qui compromettent l'équilibre lors des stimulations vestibulaires. Néanmoins, l'activité de base du triceps sural dans la position de repos évoque d'ailleurs une action de poussée vers l'avant s'opposant à une chute en arrière

Il nous est encore difficile actuellement de distinguer avec précision les caractéristiques de fonctionnement de ces muscles dans les conditions d'examen et d'enregistrement que nous utilisons.

De toute façon, alors que les déviations sont maximum, on assiste en général à une très intense activité électromyographique qui disparaît lorsque le sujet tend à revenir à sa position d'origine.

### *Electronystagmographie*

De très nettes réponses horizontales, ballant du côté opposé à l'irrigation apparaissent après un temps de latence de (2 cc) 22 sec. (4 cc) 25 sec correspondant aux temps classiquement décrits.

Elles durent en moyenne (2 cc) 63 sec (4 cc) 7 sec et donc se terminent en général avant le retour du centre de gravité à sa position initiale.

### REMARQUES

Parmi les faits les plus saillants, il faut remarquer

1 L'apparition très précoce des déviations latérales du centre de gravité qui précèdent de plus de 10 secondes les premières secondes de la réponse électronystagmographique horizontale et se prolongent en général après la fin du nystagmus.

2 Les modifications de l'activité musculaire qui, lorsqu'elles existent, apparaissent également très précocement et semblent contemporaines des déviations latérales.

Le maximum d'activité coïncide avec le maximum de déplacement et aussi avec le maximum de la réponse E.N.G.

On constate donc

1 une dissociation temporelle entre d'une part les déviations maxima du centre de gravité et les réponses musculaires associées, et d'autre part, les réponses E.N.G. horizontales

2 une plus grande précocité des déviations latérales par rapport aux déviations antérieures

3 un seuil des déviations du centre de gravité plus bas que celui du nystagmus en effet certains sujets qui n'ont pas montré de réponses nystagmiques nettes ont cependant accusé d'importantes déviations antérieures et latérales.

Quant à la déviation en az ni elle suggère que l'on stimule aussi les canaux semi-circulaires verticaux.

Néanmoins, nous n'avons pas pu mettre en évidence de nettes réponses électronystagmographiques verticales.

### DIFFICULTES ET LIMITES DE L'EXAMEN

Parmi celles-ci citon

— au 1 (âge) ne pouvant incliner la tête en arrière,

— l'instabilité des sujet non habitués à la station debout pieds nus,



- redressement progressif de la tête au cours de l'examen,
- mouvements de paupières accentués par le maintien forcé de la tête en arrière le sujet étant debout les yeux fermés
- variabilité individuelle de l'activité musculaire dans le maintien d'une position d'équilibre

Il est en outre vraisemblable que l'effort réalisé pour maintenir la tête dans la position d'examen entraîne une déviation vers le bas de l'œil qui bloque le nystagmus vertical

*Sur le plan matériel* il faut noter

- les difficultés de réglage
- l'absence de mesure quantitative des déviations,
- la nécessité 1° d'enregistrer l'électromyogramme des deux jambes car l'activité est plus grande du côté de l'irrigation et il est possible en particulier chez certains sujets que les muscles de la jambe droite aient une activité prépondérante 2° de faire l'irrigation calorique avec le plus de précision possible

### *Intérêt*

L'association de ces 3 techniques complémentaires permet

- d'effectuer une étude objective et séparée des déviations antérieure et latérale dont on remarque la grande sensibilité et la précocité par rapport à la réponse électronystagmographique
- de préciser la physiologie des muscles de la jambe et leur rôle dans l'équilibration

### SUMMARY

This study is designed to show the static modifications in patients having equilibrium troubles.

The tests are performed with or without vestibular stimulation with the aid of

- 1 A statokinesimeter with which can be recorded
  - The position of the center of gravity compared to the polygon of support.
  - Its shifting in the four cardinal directions
- An electromyograph which records simultaneously the electrical activity of some muscular groups.
- 3 An electronystagmograph

### ZUSAMMENFASSUNG

In der vorliegenden Arbeit wurde eine neue Aufzeichnungsapparatur für oto-neurologische funktionell Untersuchungen das Statokinesimeter auf ihre praktische Anwendbarkeit hin ausprobiert. Die Untersuchungen wurden an 71 normalen und pathologischen Versuchspersonen durchgeführt. Aus den gewonnenen Erfahrungen resultierte schliesslich eine Untersuchungsmethode die im wesent-

lichen auf den Ansatz lehnungen von 3 verschiedenen Einzelmomenten basiert und in detaillierter Form die Reaktion auf kalorische Vestibularstimulationen erkennen lässt.

*Clinique ORL de la Faculté de Médecine de Paris  
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## DISCUSSION

A. M. Morgan: I have been much interested in your beautiful communication. Functional exploration of vestibular nystagmus is not always easy. This method might give more reliable results in syndromes with peripheral and central elements, or poorly understood disorders, than with classic procedures of vestibular investigation.

I would like to ask whether recording of the activity of the neck muscles was part of this investigation.

M. Arslan: The findings of Mr. Platon et al. demonstrate clearly that every vestibular excitation provokes a functional variation by all the muscles of the body, as the vestibular system is strictly connected with the extrapyramidal system. This fact means that the vestibular activity is continuously checking the muscular function.

V. Torok: I want to congratulate the authors on the ingenious multiple approach for assessing vestibular activity. Nystagmus alone may not be the best measure. In certain instances, in the evaluation of the pathological vestibular nystagmus and vestibulo-spinal responses are not identical. Our experience heteropulsion is longer lasting response than nystagmus. One question I would like to ask: Is it not difficult to have a patient with disorders of equilibrium disorders to stand while nystagmus recording is carried out? This procedure requires full relaxation. On the other hand, the often apprehensive dizzy patient may not relax enough to perform Romberg test.

L. H. H. Jongkees: J félicite M. Platon et ses collaborateurs de leurs résultats avec la statokinémétrie. Je me demande si le fait que le déplacement du centre de gravité se montre avant le nystagme et disparaît après lui n'est pas causé parce qu'ils ont enregistré la phase rapide. En enregistrant la phase lente du nystagme il n'aurait probablement pas trouvé ces différences.

P. Platon (Réponse): À M. Morgan: Vous ne nous avez pas encore fait d'enregistrement des muscles de la nuque. Nous espérons que cette technique nous permettra d'établir avec plus de précision les conditions d'association clinique entre les sensations de vertige et l'absence ou la présence de nystagme.

M. Arslan: Des muscles du cou sont en effet mis en activité par une stimulation vestibulaire et jouent un rôle important dans l'équilibre. Vous espérez pour nous préciser le rôle grâce à cette méthode d'enregistrement.

V. Torok: Il est certain que le nystagmus n'est pas le seul signe intéressant à étudier et nous pensons qu'il y aura beaucoup à apprendre de l'association de ces deux registres. Quant aux difficultés, il y en a certes nombreuses. En particulier, il est remarquable que certains sujets pathologiques aient très difficiles à tenir et de tout façon cette méthode nous apporte des informations intéressantes sur le plan de la physiologie normale.

M. Jongkees: La phase lente est certainement d'une importance capitale dans l'équilibre du sujet. Les conditions particulières de ces enregistrements rendent

- redressement progressif de la tête au cours de l'examen
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*L. B. H. Jongkees:* J'écris à M. Platonov et ses collaborateurs de leurs résultats et la statistique. Je me demande si le fait que le déplacement du centre de gravité se montre sans le nystagmus et disparaît après lui n'est pas évident parce qu'il est enregistré la phase rapide. En enregistrant la phase lente du nystagmus on aurait probablement pu trouver ces différences.

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malheureusement l'étude détaillée du nystagmus difficile. De toute façon cette méthode d'examen ne peut être indiquée qu'après avoir pratiqué les épreuves vestibulaires habituelles.

The study is designed to show the static modifications in patients having equilibrium troubles. The tests are performed with or without vestibular stimulation with the aid of (1) A statokinesimeter which allows the recording of the position of the center of gravity compared to the polygon of support its shifting in the four cardinal directions and the quick correcting movements during a vertical stand of variable duration (generally one minute) (2) An electromyograph which records simultaneously the electrical activity of some muscular groups.

## GALVANIC TEST IN CENTRAL VESTIBULAR LESIONS

C. R. P. PRALTZ, M.D. and Y. KOIKE, M.D.

*From the Otorhinological Department of the University Clinic of Ear, Nose and Throat Diseases, Burgerplatz Basle, Switzerland*

1. Brainstem lesions without presence of a spontaneous vestibular nystagmus generally do not show any particular change of the pattern of the galvanic nystagmus reaction.

2. In brainstem lesions with presence of a spontaneous nystagmus the threshold of the galvanic nystagmus is mostly normal whereas supra-threshold test invariably shows a pathological reversal phenomenon. Sometimes a relatively high incidence of abnormally increased amplitude and frequency also can be found in phenomena which are not observed among other groups.

3. Cerebello-pontine angle tumours (acoustic neuroma excluded) show either a normal or a moderately raised nystagmus threshold.

4. In supratentorial lesions of the brainstem the pattern of linear and rotational galvanic responses is not characteristic.

In lesions of the cerebral cortex thresholds are normal among the majority of cases but supra-threshold test reveals relatively high incidence of pathological deviation, preponderance towards the side of the lesion which may also be combined with corresponding directional preponderance of optokinetic nystagmus.

### INTRODUCTION

Galvanic stimulation of the human vestibular system causes both a disturbance of the equilibrium and nystagmus. The fast component of poststimulatory galvanic nystagmus is directed towards the side of the negative electrode whereas poststimulatory galvanic nystagmus beats toward the positive electrode. According to the experimental findings of Ledwies (1938) this nystagmic response may be explained by an electric polarization effect of both the sensory cells of the vestibular end organ and the cells of the vestibular ganglion. The cathelectrotonus probably facilitates and increases the rhythmic bioelectric activity of the vestibular sensory and ganglion cell whereas the anelectrotonus seems to exert an inhibitory action upon neuronal activity.

The most important feature of the galvanic test is the persistence of the galvanic reaction following complete deafferentation of the vestibular endorgan and on the other hand abolition of the nystagmic response as soon as the peripheral vestibular neuron is damaged (Dahlman 1920). Hence it may

be said that the origin of galvanic nystagmus depends entirely upon the integrity of neuronal elements of the vestibular ganglion and upon the conductivity of the nerve fibers. Taking these facts into account the galvanic test is the only diagnostic procedure allowing the differentiation of an endorgan lesion from a lesion of the peripheral neuron. This test is therefore of greatest diagnostic importance with respect to the detection of an acoustic neuroma at an early stage. Owing to the lack of appropriate recording methods the properties of both per- and poststimulatory galvanic nystagmus were not well known until recently. Mainly for this reason the galvanic test has been neglected for a long time as a diagnostic procedure its results being too inaccurate to give proper information. The recording of galvanic nystagmus is made feasible only by the use of *photo-electro-nystagmography* because during galvanic stimulation nystagmography based on the derivation of corneo-retinal potentials, does not reproduce ocular movements properly but picks up a rheogram (Gabersek & Jorbert, 1965).

In previous papers (Pfaltz & Richter 1965; Pfaltz, 1965; 1967) we have tried to establish the criteria which are essential for the evaluation of a galvanic nystagmus recorded photoelectrically. Under physiological conditions *perstimulatory galvanic nystagmus* shows a rather constant pattern whereas *poststimulatory galvanic nystagmus* is more variable with respect to frequency and amplitude. For this reason we invariably evaluate *perstimulatory galvanic reactions* for diagnostic use.

In a first series of nystagmographic studies (Pfaltz & Richter 1965; Pfaltz, 1965; 1967) we have confirmed the results of Dohlmans animal experiments in normal human subjects as well as in patients suffering from vestibular disturbances of peripheral origin. In the present study we intend to investigate the problem of the diagnostic value of the galvanic test in vestibular disturbances of central origin.

#### METHODS OF RECORDING AND STIMULATION—TERMINOLOGY

The "*differential method*" of photoelectric recording of nystagmus as developed by Richter & Pfaltz (1955; 1958) works on the principle that two photoelectric cells, placed so their medial edges aim at the medial and lateral junctions of the iris and cornea respectively, with an interpose infra red light source on the pupil will record any change in the position of the eyeball by a relative change in the amount of reflected light received by each photoelectric cell. Artefacts caused by muscle tremor and by changes of the perocular electric field occurring frequently during galvanic stimulation are mainly eliminated by a photoelectric recording device.

*Bipolar-binaural galvanic stimulation* is preferred to various uniaxial and unipolar methods of stimulation because of its more constant results (Pfaltz, 1965). The intensity of the current is controlled by a milliamperè meter. The following criteria are used for the evaluation of the nystagmic response evoked by both *liminar* and *supraliminar* galvanic stimulation.

# 1 Threshold values may vary in normal individuals from 1-2 mA

Nystagmus intensity expressed by frequency (number of beats per time unit) and amplitude varies at threshold level between 0.2-1.8 jerks/second and 0.3-1.0 /nystagmus beat (normal range of distribution—statistically evaluated)

## 2 Reversal phenomenon

Every sudden change in the direction of the galvanic current 4-6 mA above threshold level instantaneously causes an abrupt reversal of the per stimulatory nystagmus. Nystagmus intensity following the reversal of the current is considerably increased 1.4-2.0 beats/second and 1.5-2.0 /nystagmus jerk (normal range of distribution—statistically evaluated) The difference between the two nystagmus reactions following the sudden change of the direction of the galvanic current should not exceed 15% of the total reaction for both frequency and amplitude.

The value of the difference (D) is calculated from the following formula

$$D\% = \frac{(a+b)}{(a+b)} \times 100$$

a = number of beat or total amplitude of left-beating nystagmus during a sample period of 10 seconds before reversal of the current (4-6 mA above threshold)

b = the same values for right-beating nystagmus

D-values exceed 15% indicate a pathological directional preponderance (statistical evaluation  $X=8.4\%$ ,  $sD=3.2$ )

## RESULTS AND CONCLUSIONS

Out of 180 cases with disorders of the central nervous system we have selected 73 patients in which an accurate diagnosis had been established with respect to the localization and the nature of the lesion either by means of a complete neurological, ophthalmological and otoneurological examination or by neurosurgical intervention and finally in some cases by autopsy. The 73 cases are subdivided into the following five groups:

- 1 Brain stem lesion without presence of spontaneous nystagmus 20 cases.
- 2 Brain stem lesion with presence of spontaneous nystagmus 20 cases.
- 3 Pontocerebellar lesion 10 cases.
- 4 Subcortical lesion 10 cases.
- 5 Cortical lesion 13 cases.

1 In lower brain stem lesions showing a rather mild symptomatology the pattern is not very characteristic but for an occasional combination of raised threshold values and normal suprathreshold reactions.

In lesions involving the pons and the midbrain area the pattern of



be said that the origin of galvanic nystagmus depends entirely upon the integrity of neuronal elements of the vestibular ganglion and upon the conductivity of the nerve fibers. Taking these facts into account the galvanic test is the only diagnostic procedure allowing the differentiation of an endorgan lesion from a lesion of the peripheral neuron. This test is therefore of greatest diagnostic importance with respect to the detection of an acoustic neuroma at an early stage. Owing to the lack of appropriate recording methods the properties of both *per* and *poststimulatory* galvanic nystagmus were not well known until recently. Mainly for this reason the galvanic test has been neglected for a long time as a diagnostic procedure, its results being too inaccurate to give proper information. The recording of galvanic nystagmus is made feasible only by the use of *photo-electro-nystagmography* because during galvanic stimulation nystagmography based on the derivation of corneo-retinal potentials, does not reproduce ocular movements properly but picks up a rheogram (Gabersek & Jorbert, 1965).

In previous papers (Pfaltz & Richter 1963; Pfaltz, 1965; 1967) we have tried to establish the criteria which are essential for the evaluation of a galvanic nystagmus recorded photoelectrically. Under physiological conditions *perstimulatory* galvanic nystagmus shows a rather constant pattern, whereas *poststimulatory* galvanic nystagmus is more variable with respect to frequency and amplitude. For this reason we invariably evaluate *perstimulatory* galvanic reactions for diagnostic use.

In a first series of nystagmographic studies (Pfaltz & Richter 1963; Pfaltz, 1965; 1967) we have confirmed the results of Dohlmans animal experiments in normal human subjects as well as in patients suffering from vestibular disturbances of peripheral origin. In the present study we intend to investigate the problem of the diagnostic value of the galvanic test in vestibular disturbances of central origin.

## METHODS OF RECORDING AND STIMULATION—TERMINOLOGY

The "differential method" of photoelectric recording of nystagmus as developed by Richter & Pfaltz (1935; 1936) works on the principle that two photoelectric cells placed so their medial edges aim at the medial and lateral junctions of the iris and cornea respectively, with an interposed infra-red light source on the pupil will record any change in the position of the eyeball by a relative change in the amount of reflected light received by each photoelectric cell. Artefacts caused by muscle tremor and by changes of the periorcular electric field occurring frequently during galvanic stimulation are mainly eliminated by a photoelectric recording device.

*Bipolar binocular galvanic stimulation* is preferred to various monaural and unipolar methods of stimulation because of its more constant results (Pfaltz, 1965). The intensity of the current is controlled by a milliamperè-meter. The following criteria are used for the evaluation of the nystagmic response evoked by both *liminar* and *supraliminar* galvanic stimulation.

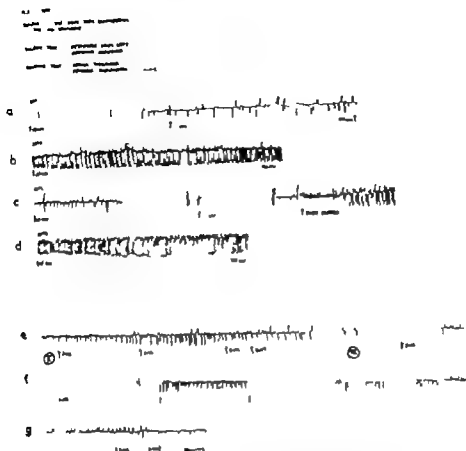


FIG. 2. a-d Cell 17 (1) No responses from left labyrinth. (e-g) Galvanic test (1) Threshold of nystagmus to the left (2 mV). (f) Threshold of nystagmus to the right (2 mV). (g) Sudden reversal of current evokes both nystagmus to the left and the right (lib. direction) perpendicular to the left, i.e. to the aid of the 1000.

ulation of gaze (Monnier 1907) show the most constant pathological findings of this particular type (Fig. 3).

Summing up our results we may conclude

(a) In cases of lesion involving the central nervous system the pattern of nystagmus following horizontal and uprollinial galvanic stimulation of the vestibular system is quite different from the pattern observed in lesions of the vestibular endorgan or its peripheral neuron.

(b) Lesion of the cerebral cortex show a pattern of the galvanic responses which is very different from those observed in brainstem lesions. Furthermore in brainstem lesions galvanic stimulation reveals again two different types of response-patterns, depending obviously upon the localization of the functional disorder. This observation is in agreement with the



2) Les lésions du tronc cérébral accompagnées d'un nystagmus vestibulaire spontané modifient la réaction galvanique différemment selon leur extension et leur caractère. Lorsque elles sont étendues et mal délimitées, le seuil du nystagmus galvanique reste normal la plupart du temps, alors que les stimulations supraliminales entraînent une augmentation pathologique de la fréquence et de l'amplitude.

3) Les tumeurs de l'angle ponto-cérébelleux n'influencent qu'un peu ou pas du tout le seuil du nystagmus.

4) Lors d'lésions supratentorielles du tronc cérébral, la réaction galvanique reste normale dans la plupart des cas.

5) Une lésion du cortex cérébral ne modifie pas le seuil de nystagmus galvanique. Le phénomène d'inversion se manifeste par contre lors de stimulation supraliminaire sous la forme d'une prépondérance directionnelle du côté de la lésion. Des lésions préventives à plus une prépondérance directionnelle du même optocinétique également dans le même sens.

### ZUSAMMENFASSUNG

1) Hirnstammläsionen ohne Anwesenheit eines vestibulären Spontan-nystagmus lassen im wesentlichen eine normale galvanische Reaktion erkennen.

2) Hirnstammläsionen mit Anwesenheit eines vestibulären Spontan-nystagmus führen zu folgenden Veränderungen der galvanischen Vestibular-Reaktion: Schwelle wird normal, überschwellige Reizung pathologisch (abnorm hohe Amplituden- und Schlagzahlwerte). In Fällen einer umschriebenen Hirnstammläsion mit galaktischer Nukleäre Facialisparese wird häufig ein Aufhebungswinkel des thermischen und des galvanischen ungelösten Nystagmus in Richtung zur Läsionsbrücke beobachtet.

3) Tumoren des Kleinhirnbrückenwinkels lassen in der Mehrzahl der Fälle entweder eine normale oder nur leicht erhöhte Vestibularschwelle erkennen während sie bei echten Akustikusneurinomen eine unnormalerweise pathologisch erhöhte ( $> 10$  mA).

4) Bei supratentoriellen Hirnstammläsionen fällt die galvanische Reaktion in der Mehrzahl der Fälle normal aus.

5) In Fällen einer umschriebenen horizontalen Läsion des Zentralorgans werden zu der Regel hin die Schwellewerte (steigend), während bei überschwelliger Reizung in der Mehrzahl der Fälle ein pathologisches Umkehrphänomen nachgewiesen werden kann. Meistens handelt es sich um ein Richtungsüberlegen des optokinetischen Nystagmus, wobei in einzelnen Fällen auch ein gleichzeitiges Richtungsüberlegen des optokinetischen Nystagmus beobachtet werden kann.

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## CHEMICAL EVALUATION OF INNER EAR FLUID AS A DIAGNOSTIC AID

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Biochemical analyses have been made of the inner-ear fluids of patients with otosclerosis, Menière's disease and acoustic neuromas. The contamination samples of perilymph removed from the vestibule of otosclerotic ears show normal values for K, Na, and protein. For Menière's disease fluid from the vestibule shows normal values for endolymph and from the scala tympani of the basal turn normal values for perilymph. For patients with acoustic neuroma, the fluid removed from the vestibule and from the horizontal canal shows very high protein values even for those patients having normal protein values in the cerebrospinal fluid. Biochemical analysis of inner-ear fluid is a useful aid for difficult diagnostic problems.

A study of labyrinthine fluid biochemistry may eventually lead to an understanding of the relationship of inner ear fluids to normal hearing function and to certain types of sensorineural deafness. The diagnostic data obtained thus far also has been of value in differentiating Menière's disease from acoustic neuroma.

A study of the chemistry of the inner ear of smaller mammals (cat) has revealed the following values:

	Sodium (meq/L)	Potassium (meq/L)	Protein (mg)
Perilymph	140	4	173
Endolymph	21	180	144
Serum	143	4	7300

These findings are in general agreement with those from other laboratories.

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## DISCUSSION

*Mr. Torok:* Mr. Pfaltz, galvanic technique offers a breakthrough in an area where up to the present we had no way to differentiate between vestibular responses. When correlated with the more routine vestibular testings and valuation the galvanic stimulation response assessed by the P.E.N.G. can differentiate location in the central nervous system which is what other vestibular assessments cannot offer.

*C. R. Pfaltz (Reply):* to Mr. Torok. The galvanic test is a complementary testing procedure which should be used together with other experimental labyrinthine tests such as thermic or rotatory stimulation. However, as pointed out before, it is a very important test for the differentiation of a lesion of the vestibular endorgan from a lesion of the peripheral neuron. As our observations have shown, the galvanic test seems also to be rather helpful with respect to the localization of a central vestibular lesion. It is the different behaviour of the galvanic response at threshold level and the one above threshold (supraliminal stimulation i.e. reversal phenomenon) which we think is of particular interest, but this is a new field of investigation and we need further information before we are allowed to draw definite conclusions.

	Case 1	Case 2
Sodium	146 meq/L	175 meq/L
Potassium	8 meq/L	7 meq/L
Protein	268 mg	325 mg

Thus, the fluid removed from the vestibule was endolymph and not altered perilymph.

The removal of perilymph from the horizontal canal of patients with proven acoustic neuromas has revealed normal perilymph values for potassium and sodium but markedly increased protein. This is consistent with the histological findings of a finely granular acidophilic staining precipitate in the perilymph of some ears with acoustic neuroma. The mean values for eleven proven acoustic neuroma cases were as follows:

Sodium	146 meq/L
Potassium	13 meq/L
Protein	1958 mg%

This elevated protein level was present in all eleven ears, five of which had normal protein values in the cerebrospinal fluid.

Diagnostic labyrinthotomies were performed on eleven patients in whom it was not possible to make a definite diagnosis between Menière's disease and acoustic neuroma. In two, the fluid from the vestibule was characteristic of endolymph and the patients subsequently were treated by labyrinthectomy with relief of symptoms. Four had greatly elevated protein levels and subsequently had successful surgical removal of acoustic neuroma by the translabyrinthine route. In five the sodium and potassium levels were normal for perilymph, however protein was slightly elevated. These patients are being kept under observation.

The diagnostic labyrinthotomy may be helpful when otologic and neurologic examination including audiometric and caloric tests, cerebrospinal fluid studies and meningeal examination fail to provide diagnostic differentiation for the patient with suspected Menière's disease or acoustic neuroma.

## RESUME

Des analyses biochimiques d'extrait d'oreille interne ont été faites sur des lésions souffrant d'otosclérose et maladie de Ménière et de neurome acoustique. Des traits de périlymphe non contaminés furent prélevés dans le vestibule lors des lésions otosclérotiques. Ils montrent des valeurs normales en sodium, potassium et protéines. Pour la maladie de Ménière les extraits vestibulaires montrent des valeurs normales pour le sodium et le potassium. La bande spectrophotométrique du tour basal des valeurs normales pour le périlymphe. Pour les malades souffrant de neurome acoustique les extraits vestibulaires et du tour basale montrent des valeurs normales de protéines dans les traits labyrinthiques. Les analyses biochimiques de l'oreille interne sont utiles dans le cas d'un diagnostic difficile.



Studies of the human ear have involved only fluid removed from the vestibule, scala tympani of the basal turn or from the horizontal semicircular canal and have been acquired from the following sources

- 1 From postmortem specimens.
- 2 During surgical procedures.
- 3 Diagnostic labyrinthotomies

Early studies revealed the importance of collecting fluids without contamination by blood or tissue fluid. Fluid was collected from the human inner ears through very small openings with the surrounding areas thoroughly dry and clean. For example, when removing fluid from the vestibule the mucosa was elevated from the footplate of the stapes, bleeding was controlled the footplate and adjacent regions were thoroughly dried with the aspiration tube and fluid was collected by capillary attraction and gentle aspiration into a micro pipette. The collection was made preferably at the level of the opening in the footplate but in no instance more than one half millimeter into the vestibule.

When collections were made by this method the values for sodium potassium and protein in ears with otosclerosis was similar to that of perilymph for lower mammals and therefore was considered to be normal. This finding is at some variance with other laboratories which have reported elevated protein values in otosclerotic ears.

The mean values for these substances in otosclerotic ears were as follows

Sodium	14 meq/L
Potassium	7 meq/L
Protein	23 mg%

Fluid removed from the vestibule by this technique from patients undergoing transmastoid labyrinthectomy for Menière's disease revealed chemical values consistent with those of normal mammalian endolymph. The mean values from fifteen patients are shown below

Sodium	20 meq/L
Potassium	160 meq/l
Protein	210 mg%

These findings are not surprising for histological studies have shown in Menière's disease that the endolymphatic system is greatly dilated with either the saccule or the herniated cochlear duct expanded to make contact with the footplate of the stapes.

The analysis of fluid taken from the scala tympani through the round window membrane in two patients revealed values for perilymph as follows

	Case 1	Case 2
Sodium	146 meq/L	175 meq/L
Potassium	5 meq/L	11 meq/L
Protein	268 mg	321 mg

Thus, the fluid removed from the vestibule was endolymph and not altered perilymph.

The removal of perilymph from the horizontal canal of patients with proven acoustic neuromas has revealed normal perilymph values for potassium and sodium but markedly increased protein. This is consistent with the histological findings of a finely granular acidophilic staining precipitate in the perilymph of some ears with acoustic neuroma. The mean values for eleven proven acoustic neuroma cases were as follows:

Sodium	146 meq/l
Potassium	13 meq/l
Protein	1020 mg%

This elevated protein level was present in all eleven ears, five of which had normal protein values in the cerebrospinal fluid.

Diagnostic labyrinthotomies were performed on eleven patients in whom it was not possible to make a definite diagnosis between Menière's disease and acoustic neuroma. In two the fluid from the vestibule was characteristic of endolymph and the patients subsequently were treated by labyrinthectomy with relief of symptoms. Four had greatly elevated protein levels and subsequently had successful surgical removal of acoustic neuromas by the translabrynthine route. In five the sodium and potassium levels were normal for perilymph, however protein was slightly elevated. These patients are being kept under observation.

The diagnostic labyrinthotomy may be helpful when otologic and neurologic examination, including audiometric and vestibular tests, cerebrospinal fluid studies and roentgenological examination fail to provide diagnostic differentiation for the patient with suspected Menière's disease or acoustic neuroma.

## RÉSUMÉ

Des analyses biochimiques d'extrait d'oreille interne ont été faites sur des malades souffrant d'otoclérose de Maladie de Menière et de neurinome. On a prélevé des extraits de périlymphe non contaminés furent prélevés de la cavité d'oreilles (cochléaires). Ils montrent des valeurs normales en sodium, potassium et en protéines. Pour la maladie de Menière les extraits vestibulaires montrent des valeurs normales pour l'endolymphe. Les patients souffrant de tumeur acoustique les extraits vestibulaires et du canal horizontal montrent des valeurs normales en sodium et potassium. Les analyses biochimiques d'oreille interne sont utiles dans le cas du diagnostic difficile.

Studies of the human ear have involved only fluid removed from the vestibule scala tympani of the basal turn or from the horizontal saccular canal and have been acquired from the following sources:

- 1 From postmortem specimens.
2. During surgical procedures
- 3 Diagnostic labyrinthotomies

Early studies revealed the importance of collecting fluids without contamination by blood or tissue fluid. Fluid was collected from the human inner ears through very small openings with the surrounding areas thoroughly dry and clean. For example, when removing fluid from the vestibule the mucosa was elevated from the footplate of the stapes, bleeding was controlled, the footplate and adjacent regions were thoroughly dried with the aspiration tube and fluid was collected by capillary attraction and gentle aspiration into a micro pipette. The collection was made preferably at the level of the opening in the footplate but in no instance more than one half millimeter into the vestibule.

When collections were made by this method, the values for sodium, potassium and protein in ears with otosclerosis was similar to that of perilymph for lower mammals and therefore was considered to be normal. This finding is at some variance with other laboratories which have reported elevated protein values in otosclerotic ears.

The mean values for these substances in otosclerotic ears were as follows:

Sodium	142 meq/L
Potassium	7 meq/L
Protein	2.3 mg%

Fluid removed from the vestibule by this technique from patients undergoing transmastoid labyrinthectomy for Meniere's disease revealed chemical values consistent with those of normal mammalian endolymph. The mean values from fifteen patients are shown below:

Sodium	29 meq/L
Potassium	160 meq/L
Protein	10 mg%

These findings are not surprising for histological studies have shown in Meniere's disease that the endolymphatic system is greatly diluted with either the saccule or the herniated cochlear duct expanded to make contact with the footplate of the stapes.

The analysis of fluid taken from the scala tympani through the round window membrane in two patients revealed values for perilymph as follows:

	Case 1	Case 2
Sodium	146 meq/L	175 meq/L
Potassium	5 meq/L	7 meq/L
Protein	208 mg	325 mg

Thus, the fluid removed from the vestibule was endolymph and not altered perilymph.

The removal of perilymph from the horizontal canal of patient with proven acoustic neuroma has revealed normal perilymph values for potassium and sodium but markedly increased protein. This is consistent with the histological findings of a finely granular acidophilic staining precipitate in the perilymph of some ears with acoustic neuroma. The mean values for eleven proven acoustic neuroma cases were as follows:

Sodium	146 meq/L
Potassium	13 meq/L
Protein	1050 mg

This elevated protein level was present in all eleven ears, five of which had normal protein values in the cerebrospinal fluid.

Diagnostic labyrinthotomies were performed on eleven patients in whom it was not possible to make a definite diagnosis between Menière's disease and acoustic neuroma. In two, the fluid from the vestibule was characteristic of endolymph and the patients subsequently were treated by labyrinthectomy with relief of symptoms. Four had greatly elevated protein levels and subsequently had successful surgical removal of acoustic neuroma by the transabyrinthine route. In five the sodium and potassium levels were normal for perilymph however protein was slightly elevated. These patients are being kept under observation.

The diagnostic labyrinthotomy may be helpful when otologic and neurologic examination, including audiometric and vestibular tests, cerebrospinal fluid studies and roentgenological examination fail to provide diagnostic differentiation for the patient with suspected Menière's disease or acoustic neuroma.

### RESUME

Des analyses biochimiques d'extraits de l'oreille interne ont été faites sur des malades souffrant d'otosclérose, de maladie de Ménière et de neurinome acoustique. Des extraits de périlymphe non contaminés furent prélevés dans le cul-de-sac de l'oreille otosclérotisée. Ils montrent des valeurs normales en sodium, potassium et protéines. Pour la maladie de Ménière, les extraits vestibulaires montrent des valeurs normales pour l'endolymphe et ceux pris dans la jampe tympanique (ou ton) basales des valeurs normales pour la périlymphe. Pour les malades souffrant de neurinome acoustique, les extraits vestibulaires et du canal horizontal montrent des valeurs normales en protéines dans les extraits de périlymphe. Les analyses biochimiques de l'oreille interne sont utiles dans le cas d'un diagnostic difficile.

Studies of the human ear have involved only fluid removed from the vestibule scala tympani of the basal turn or from the horizontal semicircular canal and have been acquired from the following sources

- 1 From postmortem specimens.
- 2 During surgical procedures
- 3 Diagnostic labyrinthotomies.

Early studies revealed the importance of collecting fluids without contamination by blood or tissue fluid. Fluid was collected from the human inner ears through very small openings with the surrounding areas thoroughly dry and clean. For example, when removing fluid from the vestibule the mucosa was elevated from the footplate of the stapes, bleeding was controlled, the footplate and adjacent regions were thoroughly dried with the aspiration tube and fluid was collected by capillary attraction and gentle aspiration into a micro pipette. The collection was made preferably at the level of the opening in the footplate but in no instance more than one half millimeter into the vestibule.

When collections were made by this method the values for sodium potassium and protein in ears with otosclerosis was similar to that of perilymph for lower mammals and therefore was considered to be normal. This finding is at some variance with other laboratories which have reported elevated protein values in otosclerotic ears.

The mean values for these substances in otosclerotic ears were as follows

Sodium	147 meq/L
Potassium	7 meq/L
Protein	223 mg%

Fluid removed from the vestibule by this technique from patients undergoing transmastoid labyrinthectomy for Menière's disease revealed chemical values consistent with those of normal mammalian endolymph. The mean values from fifteen patients are shown below

Sodium	9 meq/L
Potassium	160 meq/L
Protein	111 mg

These findings are not surprising for histological studies have shown in Menière's disease that the endolymphatic system is greatly dilated with either the saccule or the hatched cochlear duct expanded to make contact with the footplate of the stapes.

The analysis of fluid taken from the scala tympani through the round window membrane in two patients revealed values for perilymph as follows

	Case 1	Case 2
Sodium	146 meq/L	175 meq/L
Potassium	5 meq/L	meq/L
Protein	268 mg	325 mg

Thus, the fluid removed from the vestibule was endolymph and not altered perilymph.

The removal of perilymph from the horizontal canal of patients with proven acoustic neurinoma has revealed normal perilymph values for potassium and sodium but markedly increased protein. This is consistent with the histological findings of a finely granular acidophilic staining precipitate in the perilymph of some ears with acoustic neurinoma. The mean values for eleven proven acoustic neurinoma cases were as follows:

Sodium	146 meq/L
Potassium	13 meq/L
Protein	19.50 mg

This elevated protein level was present in all eleven ears, five of which had normal protein values in the cerebrospinal fluid.

Diagnostic labyrinthotomies were performed on eleven patients in whom it was not possible to make a definite diagnosis between Menière's disease and acoustic neurinoma. In two, the fluid from the vestibule was characteristic of endolymph and the patient subsequently was treated by labyrinthectomy with relief of symptoms. Four had greatly elevated protein levels and subsequently had successful surgical removal of acoustic neurinoma by the translabyrinthine route. In five the sodium and potassium levels were normal for perilymph, however protein was slightly elevated. These patients are being kept under observation.

The diagnostic labyrinthotomy may be helpful when otologic and neurologic examination, including audiometric and vestibular tests, cerebrospinal fluid studies and roentgenological examination fail to provide diagnostic differentiation for the patient with suspected Menière's disease or acoustic neurinoma.

## RESUME

Des analyses biochimiques d'extraits d'oreille interne ont été faites sur des malades souffrant d'otoclérose de maladie de Ménière et d'acurinome cochléaire. Des extraits de perilymphe non contaminés furent prélevés du vestibule d'oreilles oto-sclérotiques. Ils montrent les mêmes valeurs normales en sodium, potassium et protéines. Pour la maladie de Ménière les extraits vestibulaires montrent des valeurs normales pour l'endolympe et ceux pris dans la rampe tympanique du tour basal des valeurs normales pour le perilymphe. Pour les malades souffrant de neurinome acoustique les extraits vestibulaires et du canal horizontal montrent des valeurs normales en protéines dans les extraits cerebrospinaux. Les analyses biochimiques de l'oreille interne sont utiles dans le cas d'un diagnostic difficile.

## ZUSAMMENFASSUNG

Die Innenohrflüssigkeiten von Kranken mit Otosklerose Menièrescher Krankheit und Akustikusneurinom wurden biochemisch untersucht. Relae Perilymphe aus dem Vestibulum von Patienten mit Otosklerose ergab Normalwerte von K, Na und Eiweiß. Bei der Menièreschen Krankheit ist die Endolymphe des Vestibulums sowie die Perilymphe aus der Basilwindung der Scala tympani ebenfalls normal. Bei Akustikustumoren hingegen hat die Endolymphe des Vestibulums und des horizontalen Bogenganges einen hohen Gehalt an Eiweiß, obwohl der Liquor cerebrospinalis bei diesen Kranken normal war. Aus diesem Grunde erweist sich die biochemische Analyse von Innenohrflüssigkeiten als ein praktisches diagnostisches Hilfsmittel.

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## DISCUSSION

*v. Schullthess:* I should like to ask Mr. Schuknecht if in his cases of Menière's disease he had a relief of symptoms after creating a fistula in the footplate. Furthermore we wish to know if the author ever could find a mixture of endolymph and perilymph which would support the hypothesis advanced by him previously that the attack of Menière is produced by a rupture of the endolymphatic system.

*I. Friedmann:* Congratulations to Mr. Schuknecht. We would like to know about the origin of protein. EM studies have shown certain marked degenerative changes in the epithelium of the macula in Menière's disease. That might provide the source of protein.

*Meyer-Golltesberge:* The results at our laboratory in cases of Menière's disease agree completely with the findings of Mr. Schuknecht. In these cases we got mostly endolymph by puncture through the oval window. We have no experience in cases of acoustic neurinoma.

*G. Dohlman:* I would like to ask Mr. Schuknecht if he has taken samples of perilymph with his excellent sampling technique in the period when one would expect the electrolyte changes in connection with Menière's attack. I realize the difficulty of getting the perilymph from the pertinent area but in cases with periods of low bone impairment where theoretically you would expect a leak of endolymph through a rupture at the helicotrema it would perhaps be possible to see some potassium increase in the perilymph of scala tympani.

*L. Ruedl:* I would like to confirm the findings in Menière's disease. We found also in the fluid passed through a fistula in the footplate of the stapes K and Na values typical for endolymph. On the other hand through the round window we got in these cases K and Na values corresponding to perilymph.

*H. F. Schuknecht (Reply):* It is gratifying to learn that Mr. Meyer-Golltesberge and Mr. Ruedl have confirmed the chemical findings of vestibule fluid of ears with Menière's disease in studies performed in their laboratories. Mr. von Schullthess and Mr. Dohlman have commented on the question of the mixing of

fluids (perilymph and endolymph) during diagnostic labyrinthectomy. It is true that the theory for the etiology of the episodic vertigo in Menière's disease is rupture of the endolymphatic system. Our patients, however, had almost no reaction to diagnostic labyrinthectomy and we can only assume that the removal of fluid from the vestibule did not create mixing of fluid or severe distortion of the membranous labyrinth. Collapse of the dilated sacculus of course must take place. The cause of the low frequency deafness in Menière's disease continues to be a mystery—and possibly even more so since M. Kimura of our laboratories demonstrated that degenerative lesion of the apical region often follows destruction of the endolymphatic sac in the guinea pig. Mr. Friedmann's explanation for the elevated protein of the perilymph of patients with acoustic neuroma is also unknown. The fact that this elevation may occur in the presence of normal cerebrospinal fluid protein values indicates, however, the diagnostic value of the perilymph tap in difficult diagnostic problems.



## ZUSAMMENFASSUNG

Die Innenohrflüssigkeiten von Kranken mit Otosklerose Menièrescher Krankheit und Akustikusneurinom wurden biochemisch untersucht. Reine Perilymphe aus dem Vestibulum von Patienten mit Otosklerose ergab Normalwerte von K, Na und Eiweiß. Bei der Menièreschen Krankheit ist die Endolymphe des Vestibulums sowie die Perilymphe aus der Basilwindung der Scala tympani ebenfalls normal. Bei Akustikusneuren hingegen hat die Endolymphe des Vestibulums und des horizontalen Bogenganges einen hohen Gehalt an Eiweiß, obwohl der Liquor cerebrospinalis bei diesen Kranken normal war. Aus diesem Grunde erweist sich die biochemische Analyse von Innenohrflüssigkeiten als ein praktisches diagnostisches Hilfsmittel.

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## DISCUSSION

*v. Schullthess* I should like to ask Mr. Schuknecht if in his cases of Menière's disease he had a relief of symptoms after creating a fistula in the footplate. Furthermore we wish to know if the author ever could find a mixture of endolymph and perilymph which would support the hypothesis advanced by him previously that the attack of Menière is produced by a rupture of the endolymphatic system.

*I. Friedmann* Congratulations to Mr. Schuknecht. We would like to know about the origin of protein. EM-studies have shown certain marked degenerative changes in the epithelium of the macula in Menière's disease. That might provide the source of protein.

*Meyer-Gottesberge* The results at our laboratory in cases of Menière's disease agree completely with the findings of Mr. Schuknecht. In these cases we got mostly endolymph by puncture through the oval window. We have no experience in cases of acoustic neurinoma.

*G. Dohlman* I would like to ask Mr. Schuknecht if he has taken samples of perilymph with his excellent sampling technique in the period when one would expect the electrolyte changes in connection with Menière attack. I realize the difficulty of getting the perilymph from the pertinent area but in cases with periods of low bone impairment, where theoretically you would expect a leak of endolymph through a rupture at the helicotrema, it would perhaps be possible to see some potassium increase in the perilymph of scala tympani.

*L. Rüedi* I would like to confirm the findings in Menière's disease. We found also in the liquid gained through a fistula in the footplate of the stapes K and Na values typical for endolymph. On the other hand through the round window we got in these cases K and Na values corresponding to perilymph.

*H. F. Schuknecht (Reply)* It is gratifying to learn that Mr. Meyer-Gottesberge and Mr. Rüedi have confirmed the chemical findings of vestibule fluid of ears with Menière's disease in studies performed in their laboratories. Mr. von Schullthess and Mr. Dohlman have commented on the question of the mixing of

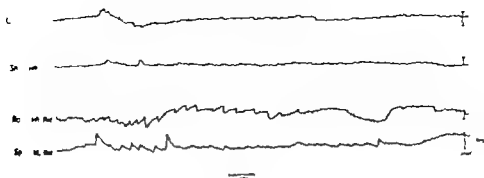


FIG. 1

movement during the stimulus and he usually was not asked to attend to his experience. This differs from the pilot of a plane who frequently initiates the stimulus with his own controls and then must purposely suppress or ignore misleading vestibular input. The habituation studies I'm about to describe deal with the earthbound simulation of a rotating space station, and in these studies the subject himself initiated the stimulus each time it occurred by a *voluntary* movement of his head.

Rotating space stations are under consideration because rotation is the simplest means of producing an artificial gravity when a person is in a weightless condition. The problem with a rotating space station lies in the fact that many people become motion sick while living in an enclosed rotating chamber and the higher the rate of rotation, the greater is the tendency to become sick. Unfortunately very low rates of rotation require very large radii to produce an artificial gravity of 1 g-unit. For example 2 rpm requires an 800-ft radius to produce 1 g-unit, whereas 8 rpm only requires a 50-ft radius. In the process of determining how people adjust to a continuously rotating environment, we have found some interesting modifications of vestibular reaction which I'm going to describe today.

We have done experiments in which rates of rotation were varied between 1 and 10 rpm with men living in the rotating room for as long as several weeks (Graybiel *et al* 1960 Guedry 1963 Guedry & Graybiel 1962). For some time after rotation commences, each head movement induces an unusual sensation. For example rotating the head forward produces a sensation, not of forward rotation, but of lateral rotation of the head and body. Nystagmus in a plane at right angles to the head movement may also be recorded. As few as three or four head movements while rotating at 10 rpm will make sick some sensitive men. However most of our subjects have shown an ability to habituate to this environment. This habituation becomes manifest in several ways. During prolonged exposure most men have reported that the misleading sensations, the nystagmus, the nausea and motion sickness diminished or disappeared. However after

## SOME VESTIBULAR PROBLEMS RELATED TO ORIENTATION IN SPACE

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Aircraft and spacecraft introduce unnatural combinations of vestibular and visual stimuli. Many of these situations produce spatial disorientation and performance degradation which can be anticipated by knowledge of the mechanics of vestibular stimulation. Experiments to test predictability of reactions to unnatural vestibular stimuli have contributed to current knowledge of vestibular function. Some of these experiments are reviewed to illustrate methods employed for the assessment of vestibular function and to illustrate implications of the results for spatial orientation and theory of vestibular function.

### INTRODUCTION

Aircraft and spacecraft are capable of producing vestibular stimulation which can be highly disturbing to flight personnel. I am going to review briefly some of our research in three general problem areas: (A) Habituation to unusual vestibular stimulation; (B) interactions between linear and angular accelerations in controlling the dynamics of spatial orientation; and (C) visual acuity during strong vestibular stimulation.

### RESEARCH ON VESTIBULAR FUNCTION IN RELATION TO PROBLEMS OF AEROSPACE FLIGHT

A *Habituation to unusual vestibular stimulation* has been revivied as an area of special interest since the advent of the space age. Most men are habituated to the vestibular stimulation which accompanies natural movement and even the unnatural movement of our many land vehicles. The reflex activity and sensations which are set off in these situations are appropriate and hence beneficial to coordinated movement. However, unusual maneuvers of certain air and spacecraft introduce vestibular stimulation which is sometimes incapacitating.

There is a distinction which I think is important between the habituation I'll describe today and a number of recent habituation studies. Many habituation studies have consisted of repetitive passive rotation of a restrained animal or man. The test subject was not trying to control his

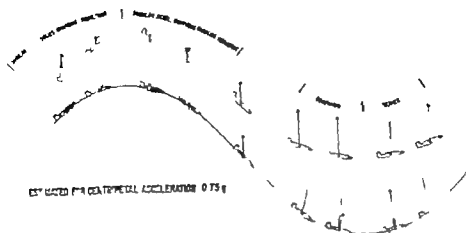


FIG. 6.

less steep climb than is actually occurring, and hence they tend to pull up too fast. Here the magnitude of the resultant force is probably so great as to override angular acceleration stimulus to the canals and the misleading direction of the resultant force misleads the pilot.

C. The ability to see during and after recovery from a turn or spin is the third area of experimentation I'd like to describe. During a turn or spin, vestibular nystagmus may aid visibility of the earth, but it will interfere with visibility of flight instruments in the cockpit. Cessation of a rapid spin or spiral of several turns can produce a false sense of reversed spinning and blurred vision of cockpit and earth, all of which jeopardizes aircraft control (McIvill Jones, 1937). The question is: What is the strength of the vestibular stimulus required to degrade cockpit vision, and how much do people differ in this regard?

To investigate this, we used pilot candidates, all with good static visual acuity and required them to identify sets of visual targets graduated in size during and after prolonged angular acceleration (Guedry 1967). Prolonged accelerations were used to provide time for visual judgments.

Some of the results are shown in Fig. 6, where arrows designate the beginning and end of a 12 second interval of  $30 \text{ deg/sec}^2$  angular acceleration. Dots below the individual nystagmus tracings show when the subject signaled loss of sets of visual targets.

Just after the last dot to the right designating loss of the largest target set an abrupt increase in nystagmus amplitude occurs. This amplitude change seems to indicate the point of surrender of voluntary efforts to maintain visual suppression of nystagmus, and it is not accompanied by a comparable increase in nystagmus slow phase velocity. However, before this amplitude change there are successive step-like increases in slow phase velocity which seem to correspond to the loss of successively larger target sets.

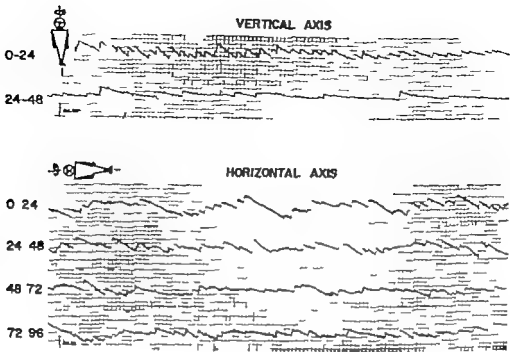


FIG 4

each case (Guedry 1965). This response about the horizontal axis is accompanied by a sensation of continuous rotation in normal men when the rotation rate is 10 rpm or less. In people without inner ear function neither the continuous sensation of rotation nor the unidirectional nystagmus occurs. When the rate of rotation is 30 rpm, the unidirectional nystagmus disappears after the angular acceleration, and the sensations reported by normal men are the same as those reported by men without labyrinthine function (Correia & Guedry 1966). From this and related research (Benson & Bodin, 1965; Benson & Whiteside 1961; Guedry 1966; Guedry & Harris, 1963; Lansberg *et al.*, 1965) I have become increasingly convinced that an understanding of dynamic spatial orientation requires consideration of the combined action of canals and otoliths and that the separate consideration of the function of canals and otoliths can be misleading.

Now let us look at a situation in flight illustrated in Figure 5 which is probably influenced by these effects. In a climb and dive maneuver the resultant at the beginning of the pushover shifts in a direction which would make the pilot experience a nose-up attitude greater than is actually the case, but here the angular acceleration would contraindicate this change in attitude. Hence the perceptual error at the beginning of the maneuver should be diminished. However, as the pilot continues the pushover maneuver the resultant shifts to make the pilot experience a steeper dive than is occurring and furthermore now the semicircular canal information confirms the change in resultant. Hence the perceptual error could be great. In fact pilots don't have trouble in the beginning of the pushover but they do experience a too-steep drive. In the pullup they experience a

## NYSTAGMUS

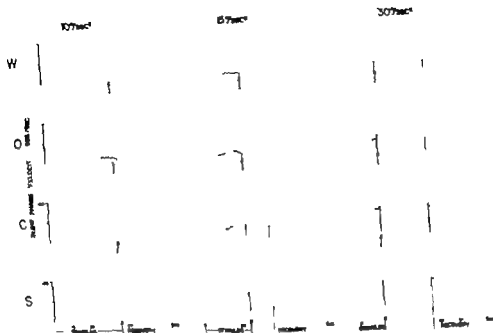


FIG. 8.

proceeded in step-like fashion. Apparently visual suppression could effect a step-like drop in nystagmus velocity only after vestibular input declined to a certain level. In other words during the recovery when eye velocity declined to permit registration of some minimal visual pattern visual suppression could effect a step-like decline in nystagmus slow phase velocity.

Fig. 8 is also sufficient to show the magnitude of individual differences among pilot candidates with equal and good static visual acuity. Subject S with the weakest stimulus had much more nystagmus than subject W with the strongest stimulus, and the visual performance of S with the weakest stimulus was inferior to that of W with the strongest stimulus. Considering the 10 deg/sec² stimulus, W maintained essentially normal vision while S became virtually blind for visual detail.

Further checks of 17 subjects revealed that there were significant correlations between visual acuity scores and nystagmus scores and that these were about equivalent to correlations between two sets of nystagmus scores. Nystagmus recorded in darkness was significantly correlated to nystagmus recorded in the light and both were correlated to visual acuity scores. In other words, the scores of an individual on one of these measures could be used to predict fairly well his scores on the other measures.

The plots presented in Fig. 8 were made by an electromechanical slope computer were developed (Guedry & Turnipseed, 1967). Recently there

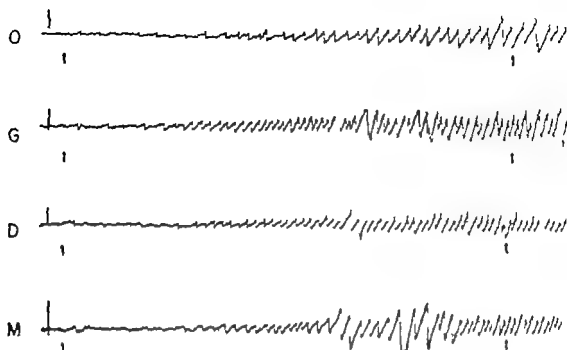


FIG. 6.

The average rise curve of eye velocity plotted with respect to time during the visual task differs in shape from the negative exponential rise curve expected from mechanics of the cupula endolymph system as described by van Egmond *et al* (1949). This is shown in Fig 7 where the dots are average eye velocities obtained during a 30 deg/sec- stimulus. Individually scored records suggest that this pronounced departure from the "expected" curve is attributable to the averaging of step-like increments in velocity which in turn were accentuated by the visual suppression.

These step-like rises in slow phase velocity can be seen in Fig 8 which shows individual results of subjects W, O, C and S during and after angular accelerations of three magnitudes. These step like increases in nystagmus velocity seem to mark levels of vestibular activity which overcome limits of visual suppression for different size targets. The nystagmus decay also

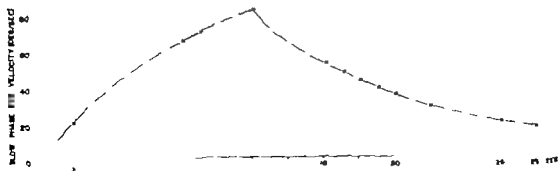


FIG. 7.

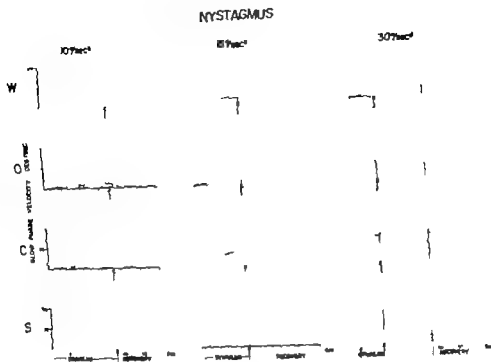


FIG. 8.

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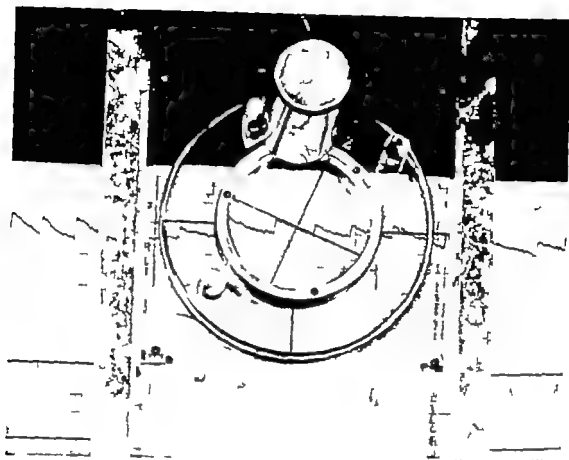


FIG 9

seems to be an increase of interest in the scoring of nystagmus and for this reason I'll describe this device we're using very briefly

As the dial shown in Fig 9 is turned until the crosshairs and nystagmus slope match a potentiometer supplies a voltage which is converted by a function generator into angular velocity. Another potentiometer supplies a voltage proportional to time. A digital voltmeter prints out the nystagmus velocity and time of each beat while an X-Y plotter plots the analog display. The individual graphs present in Fig 11 were obtained directly from the X-Y plotter. Hence our records are measured, tabulated and plotted much faster than measurement alone was previously accomplished. (See also Benson & Stuart 1966)

### RÉSUMÉ

L'avion et la cabine spatiale nous ont confrontés avec des combinaisons inhabituelles de stimulus vestibulaires et visuels. Ces situations causent fréquemment une désorientation et une dégradation dans les performances qu'on peut prévoir par la connaissance du fonctionnement de l'appareil vestibulaire. L'étude des réactions à une stimulation vestibulaire inhabituelle a complété nos con-

salvances actuelles du système vestibulaire. On ignore une de ces expériences concernent des combinaisons d'accélération linéaire et angulaire. Celles-ci sont utilisées dans l'examen vestibulaire afin de trouver leurs implications quant à l'orientation dans l'espace. Quant à la théorie de la fonction vestibulaire.

## ZUSAMMENFASSUNG

Flugzeuge und Raumschiffe erzeugen unnatürliche Kombinationen vestibulärer und Schreize. Viele dieser Bedingungen sind begleitet von räumlicher Disorientierung und verringerter Leistungsfähigkeit, die vorausgesehen werden können wenn der Mechanismus der vestibulären Funktion bekannt ist. Einige dieser Experimente die sich auf spezielle Kombinationen linearer und Winkelbeschleunigungen bezogen, werden untersucht um die Methoden der Auswertung vestibulärer Funktion und die Folgerungen der Ergebnisse für die räumliche Orientierung und die Theorie der vestibulären Funktion zu illustrieren.

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Pensacola Fla USA

## DISCUSSION

*M Borgeat* I was very much interested by Mr Guedry's communication. Indeed as far as nystagmus is concerned, we have found also on small animals that after intermittent rotation around the vertical axis of the labyrinth the nystagmus response shows a very important diminution which takes several days to recover if it does. Also with the financial help of the french national defense office we have built a machine in order to study more precisely these phenomenon by rotation in the 3 axis and recording of different biological responses and physical parameters at the same time.

*L B W Jongkees* I congratulate Mr Guedry on his remarkable contribution. I have some questions and remarks.

(1) The adaptation to complicated Coriolis stimuli has already been described by Groen before the Collegium. Groen found a great habituation to the movements of ships at sea and called this "pattern building".

(2) Could Mr Guedry comment on Benson's "slosh" theory?

(3) The equation for endolymph-cupula movements proposed by Edmond, Groen & Jongkees, is only valuable during the first seconds of stimulation. After about 15 sec the canal stimulation has completely stopped. The effects found during constant acceleration must be due to visual stimulation a canalicular factor in them is impossible.

*F E Guedry (Repl)* to Dr *Borgeat* I am quite interested in the work you described related to our experiments. I believe that there may be an important distinction between (1) repetitive vestibular stimulation of a restrained animal or man who does not produce the stimulus by his own actions and (2) our experiments in the rotating room in which subjects introduced the stimulus by voluntary head movements. This may produce different results than repetitive passive stimulation.

to Mr *Jongkees* Regarding his comments on adaptation I am familiar with Groen's "pattern copy" hypothesis to explain "sea legs" etc. It seems to me that our results are in support of this general theoretical position and our records of nystagmus produced by head movements after subjects leave the rotating room are objective support.

In regard to Mr *Jongkees* comment on the Benson "slosh" theory—this refers to one of several ideas Alan Benson had in regard to possible explanations of the prolonged unidirectional nystagmus present during rotation about a horizontal axis. Basically the idea is that a difference in specific gravity of endolymph and perilymph could cause a pumping action by virtue of a traveling deformation around the membranous canal. In an experiment involving record

ings in the vestibular nuclei of cats from units which seemed to have their origins in the horizontal canals, Melvill Jones, Benson and I found evidence which seemed to support this notion. However all of us still regard this idea as speculation.

In regard to the fact that the torsion pendulum analogy does not predict very well with prolonged vestibular stimulation, i.e. more than 10 sec, I am in agreement. Subjective sensations of rotation decline during constant angular acceleration and show earlier departures from the theoretical curve than do nystagmus responses. I have reported experiments which illustrate these departures from the "torsion pendulum theory".

## NYSTAGMIC CORIOLIS REACTION IN THE CAT

### *I Preliminary Report*

C. FERNÁNDEZ, M D and M VALENTINUZZI M D

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A series of cats with normal ears and with unilateral labyrinthectomy were exposed to Coriolis acceleration by simultaneous rotations of constant angular velocity about a vertical and horizontal axis. In both sets of animals, the results were in agreement with predictions formulated by the labyrinthine kinematics of Coriolis acceleration. The recordings showed that in both horizontal and vertical leads two reversals in the direction of nystagmus occurred for each oscillation of the Coriolis acceleration. The infra red films demonstrated that the direction of nystagmus changed orderly for each oscillation of Coriolis acceleration. A phase difference between this oscillation and reversals of nystagmus was found. The phase difference was shifted as a function of angular velocity about the horizontal axis.

The kinetics of the cupula-endolymph system under Coriolis acceleration has been described in detail by a number of investigators (Schubert, 1932 Meda 1952 Bornschein & Schubert 1958 Guedry & Montague 1961 Hixson Niven & Correia, 1966 Valentinuzzi 1967 and others). The theoretical considerations have predicted and then confirmed experimentally the subjective and nystagmic aspects of the vestibular Coriolis reaction in man. In the guinea pig, Bornschein & Schubert (1958) demonstrated similar nystagmic effects. The experiments reported here were designed for the purpose of observing the vestibular Coriolis reaction in normal and in unilateral labyrinthectomized cats. In this preliminary report the evaluation of the findings is presented in a qualitative form.

### METHODS

The experiments were carried out in eleven normal and in ten unilateral labyrinthectomized cats. The testing of the latter was done after the vestibular disorder had compensated that is, in 30 or more days after the operation.

This work was supported by Grant NB-1220-10 from NIH and AF 41(600) 2768 from School of Aviation Medicine San Antonio, Texas.



FIG. 1. The upper photograph shows the cat with implanted electrodes for recording horizontal and vertical components of nystagmus. The lower photograph shows the cat with permanently implanted electrodes and plug-in.

Insert drawing. The screw *A* is made of glass (2.7 mm diameter) with central perforation into which isolated lead is inserted (plastic Vaseline coating). The tip, *B*, of isolated lead, *L*, is made of silver wire which fits tightly into the screw perforation. The permanent lead of cement machine is inserted into the skull with two metal screws. It is essential that the individual leads in *B* be soldered to the same pin of the socket.

tion. Silver wire electrodes were implanted in the external canthi of both orbits and in the upper and lower ridges of the right orbit (Fig. 1) for recording the horizontal and vertical components of nystagmus respectively. The isolated lead and reference lead were soldered to a 5-pin subminiature socket which was cemented to the skull. The skin was sutured over the leads and around the socket. These electrodes remained in place for months without complications. The corneoretinal potential and angular velocity of the rotating devices were recorded by conventional DC coupling methods (Offner Dynograph, Type R model). We found that under our experi-

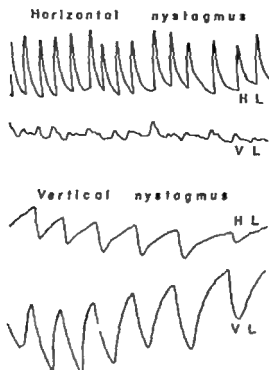


FIG. 2. Records of a horizontal and vertical nystagmus as recorded by horizontal (H.L.) and vertical (V.L.) leads. The recording of a pure horizontal nystagmus by the vertical leads may be due to a number of causes such as unfavorable orientation of the ocular bioelectric field relative to the recording electrodes. Similar causes may result in recording vertical nystagmus by the horizontal lead.

mental conditions, the vertical leads recorded distinctly a pure horizontal nystagmus although its amplitude was small. Similarly, pure vertical nystagmus had been recorded distinctly by horizontal leads (Fig. 2).

The cat was immobilized in an animal box as described elsewhere (Henrikson, Fernández & Kohut 1961). The box was fixed to the ring of a superstructure mounted upon a turntable (Fig. 3) so that the plane of the horizontal canal was oriented on the Earth horizontal plane. The three cardinal axes, relative to the head of the animal, intersected approximately at a point midway between the two ears. The turntable and ring of the superstructure rotated independently and simultaneously in a clockwise or counterclockwise direction according to a pre-set program. The turntable rotated about the  $y$  axis while the ring of the superstructure rotated about the  $x$ -axis of the cat. In static conditions during rotation of the ring both  $y$  axis and  $x$ -axis of the cat were continuously changing their spatial orientation relative to the respective axes of the turntable.

The testing of the cat consisted of three stages. First, the turntable was rotated at constant angular velocity  $\omega_p$  for one minute before starting rotation of the ring about the  $x$ -axis. This interval was considered sufficient to eliminate any effects produced by the initial acceleration of the turntable. Second, the ring of the superstructure was rotated at constant angular velocity  $\omega_r$  for ten complete turns about the  $x$ -axis. Third, the turntable

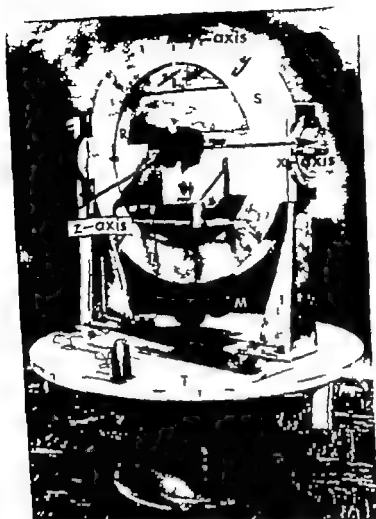


FIG. 3 Photograph of the rotatory device with cat mounted on it. The turntable, *T*, is mounted on large diameter shaft which is directly coupled to DC torque motor and DC tachometer (Inland Controls, Precision Rotational System, Model 722). The superstructure, *S*, contains rotating ring, *R*, which is coupled by belt to DC motor *M*. The cat is mounted on platform attached to *R*. The leads, *L*, are connected to the shaft of the turntable and by slip rings to the input leads of the Dynagraph. The three cardinal axes are drawn relative to the cat's head. The *y*-axis is coincident with the *y*-axis of the turntable. At rest, the horizontal *xz* plane lies on the Earth-horizontal plane. Rotation about *y*-axis is referred to the *y*-axis of the turntable while rotation about the *x*-axis is always referred to *x*-axis of the cat.

continued rotating about the *y*-axis for one additional minute. The testing was done in total darkness. The animal was not tested oftener than every eight days and each testing period consisted of three to six runs each, repeated at 15 minute intervals. In these sessions either the angular velocity  $\omega_y$  was maintained constant while  $\omega_x$  was varied, or vice versa, or



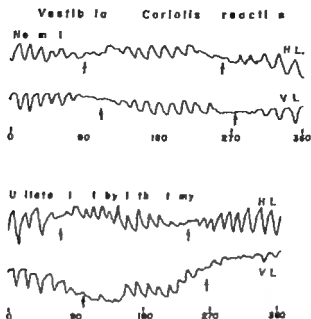


FIG. 5. Nystagmi Coriolis reaction. H.L., horizontal leads; V.L., vertical leads. The cat was rotated clockwise at  $\omega = 80$  deg/sec and  $\omega = 28$  deg/sec. The cat with bilateral labyrinthectomy was also rotated clockwise at  $\omega = 80$  deg/sec and  $\omega = 30$  deg/sec. The arrows point to the area where reversals of nystagmus occur. The phase difference between reversals from horizontal and vertical leads is demonstrated. The pattern of nystagmus of the normal animal is similar to that of the cat with unilateral labyrinthectomy. The reversals in the vertical lead are lagging the reversals of the horizontal lead.

### Vestibular Coriolis reaction

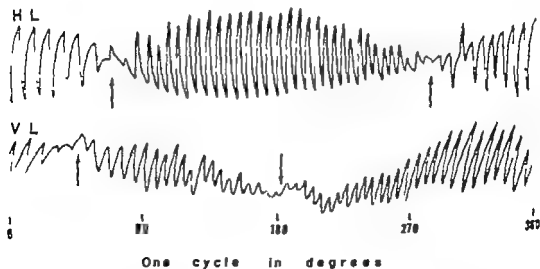


FIG. 6. Records illustrating the reaction of vestibulo Coriolis reaction in a cat with clockwise rotation about both y-axes at  $\omega = 80$  deg/sec and  $\omega = 30$  deg/sec. H.L., horizontal leads; V.L., vertical leads. The figure shows the nystagmus of the third cycle about  $\omega = 1$ . The arrows point to the area of reversal. In this run the reversal of the horizontal lead are lagging the reversals of the vertical leads.

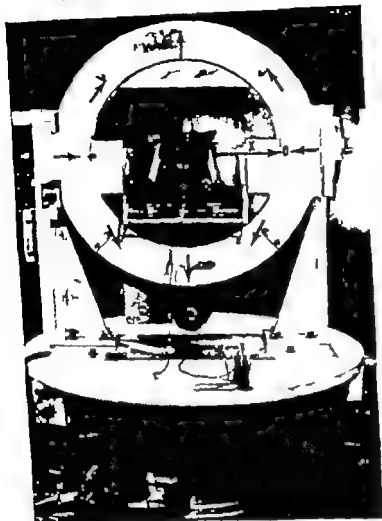
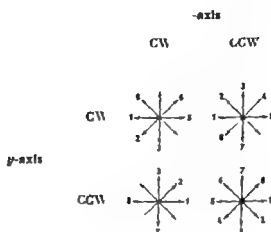


FIG. 7. Vectorial representation of the periodic Coriolis star nystagmus. The cat was rotated clockwise about both  $y$ -axis and  $z$ -axis ( $\omega_y = 80 \text{ deg/sec}$ ,  $\omega_z = 80 \text{ deg/sec}$ ). The arrow  $\gamma$  indicates the  $x$ -axis of the cat. The vectorial presentation of nystagmus relative to the head of the cat is indicated by arrows on the frame of the superstructure. As the  $z$ -axis rotates clockwise the direction of the sequential change in the vectors is counterclockwise. Notice that magnitudes of the vectors are equally represented although the oblique vectors may be somewhat smaller.

towards the forehead of the cat respectively. In between these positions the direction of the nystagmus was bilquid as shown in the figure. No rotatory component was ever observed in the infra red films. The vector of the periodic Coriolis star nystagmus changed according to clockwise or counterclockwise rotation about the  $y$ -axis or  $z$ -axis, as shown in Table 1. When the rotation about both  $y$ -axis and  $z$ -axis was clockwise, the nystagmic vector rotated counterclockwise. A clockwise rotation about the  $y$ -axis and

TABLE 1 Vectorial presentation of the fast phase of the periodic Coriolis nystagmus as a function of simultaneous rotation about the  $y$ -axis and  $z$ -axis.

The frame of reference is the head of the cat. Then numbers indicate the sequence of nystagmic vectors as the cat rotates 360 deg. about the  $z$ -axis. The equal magnitude of the vectors is arbitrary.



counterclockwise rotation in the  $z$  axis produced clockwise rotation of the vector. The table indicates the sense of the nystagmic vector for the four combinations of rotations about  $y$  axis and  $z$  axis. The form, horizontal or vertical nystagmus, the direction and the change of the nystagmic vector can also be determined on the recordings.

The first reversal of the nystagmus during a complete cycle of the ring of the superstructure occurred between 0 and 180° while the second reversal was found between 180 and 360°. For one set of conditions, the phase difference,  $\varphi$ , between 0° and first reversal was of about the same magnitude as that between 180° and second reversals. The value of  $\varphi$  however changed as a function of  $\omega$ , that is, for a fixed value of  $\omega_y$ , the phase angle,  $\varphi$ , was displaced progressively with increased value of  $\omega$  (Fig. 8). This shift appeared in both the horizontal and the vertical leads. On the other hand, for a constant value of  $\omega_y$ , the increase of  $\omega_z$  was associated with no change of  $\varphi$  (Fig. 9).

The two sets of leads recorded eye movements of similar pattern that is, between two consecutive reversals, the amplitude of nystagmus was first small, increased to a maximum and then diminished until it disappeared. The infra red film showed eye movements of about the same amplitude in the horizontal and vertical planes while oblique jerks were somewhat of smaller amplitude. This pattern was repeated from one cycle to another and under all combinations of  $\omega_y$  and  $\omega_z$  which were used.

The frequency of the nystagmus in both leads seems to be a function of both  $\omega_y$  and  $\omega_z$ . Apparently the frequency increased with  $\omega_z$ .

The velocity of slow phase of nystagmus appeared as a linear function

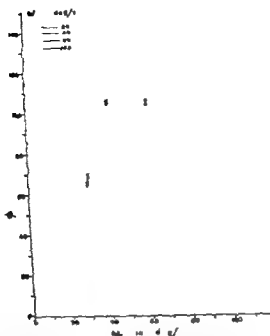


FIG. 2. Phase difference  $q$  between Coriolis acceleration and reversal of nystagmus plotted function of  $\omega$ . The measurements were made in the record from horizontal leads. For each cycle about the  $\omega$  is, the phase differences of first and second reversals to  $0^\circ$  and  $180^\circ$  respectively were measured and averaged. These averages of the ten runs of each session were added and the average calculated. The latter is represented by the point on the graph. The data for different values of  $\omega$ , are represented by symbols. The figure illustrates the trend of  $q$  to increase as  $\omega$  increases.

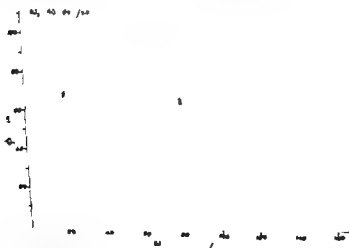


FIG. 3. The phase difference,  $q$  of reversal of nystagmus plotted function of  $\omega$ . The data are calculated as described in Fig. 2. There is scattered  $q$  of the points, but the general trend is toward constant  $q$  including the highest value of  $\omega$ .

of  $\omega$ , for values up to 160 deg/sec. No higher values have been used because of instrumental limitations. So far the data indicated a non linear relationship between speed of slow phase and  $\omega$ .

### DISCUSSION

The experimental findings presented in this preliminary report are predictable from the kinematics of the cupula-endolymph system exposed to rotation about two orthogonal axes. We only like to emphasize a few points in order to understand the stimulation under our experimental conditions.

The theoretical considerations postulate that simultaneous rotation at constant angular velocity about a  $y$  axis and a  $z$  axis results in a Coriolis acceleration of different magnitudes around the circumference of the endolymphatic rings. Thus, the endolymph must move according to the effective resultant of the inertial torque. The theory has predicted that the resultant is an oscillation following a sine function in the horizontal canals while in the vertical canals follows a cosine function. Consequently the endolymphatic currents must follow similar functions. The magnitude of the effective resultant torque is a function of  $\omega$  (Bornschein & Schubert, 1958; Valentinuzzi 1961). If the cupula-endolymph system follows the oscillation of the torque then the endolymphatic currents must change their direction twice during one complete oscillation of the resultant. Accordingly the nystagmus associated with the displacements of the cupula-endolymph system must reverse its direction twice during one oscillation of the resultant. Our experimental findings clearly demonstrated that this was the case. Furthermore, the theory also predicts that the duration of one oscillation of the resultant torque is a function of  $\omega$  and therefore, during this time only two reversals should occur. The experimental findings confirmed this prediction since an increase of  $\omega$  up to 160 deg/sec was consistently associated with only two reversals of nystagmus during any complete rotation about the  $z$  axis.

The theory that the cupula-endolymph system of the semicircular canals behaves as a highly damped torsion pendulum (Steinhausen, 1931; van Egmond, Groen & Jongkees, 1949; Groen, Löwenstein & Vondrik, 1952) accounts for the phase difference between reversals of nystagmus and oscillation of Coriolis acceleration. The increase in this phase difference as function of  $\omega$  still requires further analysis.

The estimates of the intensity of the nystagmic Coriolis reaction as determined by the speed of the slow phase of nystagmus indicated a nonlinear relation with  $\omega$  for the range used in our experiments. Because of instrumental limitations we have no information about intensity of nystagmus for values of  $\omega$  higher than 160 deg/sec. On the other hand, the data showed that the speed of the slow phase followed a linear relation to  $\omega$ .

The form and direction of nystagmic Coriolis reaction is also predicted from the theory. Let us consider the  $x$ -axis of the animal (Fig. 7) passing

through 0 at constant angular velocity in a clockwise direction. If the damping of the cupula-endolymph system is considered, then the kinematics of Coriolis acceleration shows a torque acting upon the endolymphatic ring producing an ampullopetal flow in the right horizontal canal and an ampullo-fugal flow in the left horizontal canal. Therefore the nystagmus must be toward the right of the animal as shown by the infra-red film. The same theoretical considerations about the torque in other positions predict accurately the direction of nystagmus. These calculations are considerably facilitated by using models or anatomical preparations of the cat's skull. The analysis of the kinematics of Coriolis acceleration acting upon the vertical canals also predicts the sequential change in direction of the "periodic Coriolis star nystagmus" from a horizontal to a vertical direction. This was demonstrated in the infra-red films.

The pattern of electronystagmogram regarding amplitude of nystagmus also can be predicted from the kinematics of Coriolis acceleration. The amplitude measurements of nystagmus between two reversals as shown for instance, by the horizontal leads of Fig. 8 revealed a progressive increase to a maximum and then decrease until it disappeared. The increase and fading of the amplitude of the recordings are due to displacement of the cupula-endolymphatic ring and to the change in direction of the bioelectric field as the nystagmic jerks approach and then pass the horizontal plane of the cat. The horizontal electrodes only record the horizontal component of this bioelectric field.

It was not surprising to find that the "periodic Coriolis star nystagmus" of cats with unilateral labyrinthectomy was similar to that of normals. The similarity is related to the neural mechanism underlying vestibular compensation which was already established in our animals. Under this condition the vestibular reaction produced by stimulation of the remaining labyrinth can hardly be differentiated from that of a normal cat.

As a last commentary we would like to point out that the role of the otolithic system in the nystagmus of the vestibular Coriolis reaction is not known. The magnitude of the Coriolis acceleration under our experimental conditions seems to be small as compared with the acceleration of gravity. The same conclusion was reached by Guedry & Montague (1961) in their experiment with man. This speculation however requires further experimentation.

## RESUME

Une série de chats avec oreilles normales et avec labyrinthectomie unilatérale ont été soumis à une accélération de Coriolis par rotations simultanées à vitesses angulaires constantes autour d'un axe vertical et d'un axe horizontal. Dans les deux groupes d'ensemble les résultats ont été d'accord avec les prédictions formulées par la cinématique de l'accélération de Coriolis. Les enregistrements ont montré dans les électrodes horizontales et verticales deux renversements de la direction du nystagmus pour chaque oscillation de l'accélération de Coriolis. Les

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The estimates of the intensity of the nystagmic Coriolis reaction as determined by the speed of the slow phase of nystagmus indicated a nonlinear relation with  $\omega$  for the range used in our experiments. Because of instrumental limitations we have no information about intensity of nystagmus for values of  $\omega$  higher than 100 deg/sec. On the other hand the data showed that the speed of the slow phase followed a linear relation to  $\omega$ .

The form and direction of nystagmic Coriolis reaction is also predicted from the theory. Let us consider the  $x$  axis of the animal (Fig. 1) passing

through 0 at constant angular velocity in a clockwise direction. If the damping of the cupulo-endolymph system is considered, then the kinematics of Coriolis acceleration shows a torque acting upon the endolymphatic ring producing an ampullopetal flow in the right horizontal canal and an ampullo-fugal flow in the left horizontal canal. Therefore the nystagmus must be toward the right of the animal as shown by the infra-red film. The same theoretical considerations about the torque in other positions predict accurately the direction of nystagmus. These calculations are considerably facilitated by using models or anatomical preparations of the cat's skull. The analysis of the kinematics of Coriolis acceleration acting upon the vertical canals also predicts the sequential change in direction of the "periodic Coriolis star nystagmus" from a horizontal to a vertical direction. This was demonstrated in the infra-red films.

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## RESUME

Ces séries d'expériences ont été réalisées avec des oreilles normales et avec labyrinthectomie unilatérale. Elles ont été soumises à une accélération de Coriolis par rotations simultanées à vitesses angulaires constantes autour d'un axe vertical et d'un axe horizontal. Dans les deux groupes d'animaux les résultats ont été d'accord avec les prédictions formulées par la cinématique de l'accélération de Coriolis. Les enregistrements ont montré dans les électrodes horizontales et verticales deux renversements de la direction du nystagmus pour chaque oscillation de l'accélération de Coriolis. Les



priaz kinematograficheskikh infra-krasnykh ont dmonstrirovali, chto napravleniye nystagmusa izmenyetsya sponosobno poriadkovanno dlya kazhdoy otklonyeniya ot uskoryeniya Coriolisa. Ona naiznashchena raznitsa fazy mezhdu etoy otklonyeniya i obrashcheniyami nystagmusa. Raznitsa fazy byla raznyaya v zavisimosti ot uglovykh skorosti okolo gorizontal'noy osi.

## ZUSAMMENFASSUNG

Normale und labyrinthektomierte Katzen wurden fortgesetzten periodischen Coriolis-Beschleunigungen unterworfen. Dieses ergab periodische Schwankungen im Umfang einer Winkelverschiebung zwischen beiden Komponenten einer winkelige Phase zwischen Coriolis-Beschleunigung und Reaktion, eine Beeinflussung der Geschwindigkeit der senkrechten Rotation auf die Reaktionsstärke und Umkehrungen der Richtung im Verhältnis zu den Umkehrungen der Coriolis-Beschleunigung.

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## DISCUSSION

*L. B. W. Jongkees* I would like to know the time constant of this recording apparatus.

*M. Burgeat* Did you find as well a diminution of the E.N.G. responses after repeated rotations?

*L. B. W. Jongkees* I would like to know the time constant of this recording apparatus.

*C. Fernandez* (Reply) to Mr. *Burgeat* In our experiments it was found that repeating the rotation about the two axes was associated with rapid habituation. The frequency and amplitude of the periodic Coriolis star nystagmus diminished significantly after two or three runs as explained in the method of our work. For this reason the animals were tested at intervals of eight or more days.

to Mr. *Jongkees* All the recording was done with DC coupling

## COMPUTER ANALYSIS OF ELECTRONYSTAGMOGRAPHIC DATA

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Electronystagmographic data obtained in the usual way by calorization are recorded on magnetic tape in analog form. The answers are then digitized and fed directly to a digital computer for analysis. The analog tapes have control pulses whereby it is possible to select separate data for any patient on the tape. The programs used now calculate frequency amplitude differentiated response and duration etc., in order to evaluate the possible clinical use of the automatic procedure.

A system has been devised for converting nystagmograms or other experimental data, originally recorded on magnetic tape in analog form, to digital form with a variable sampling rate.

The system is flexible so that it is possible not only to search for a particular recording on the tape but also to transfer any selected part of it to the computer. The transfer to the computer is entirely controlled by the user through certain control parameters to the reading programs. The construction of the electronic connection to the computer permits also the use of tape recorders which might cause interfering pulses on starting and stopping.

The system has been used for an automatic analysis of electronystagmograms recorded in the ENT-clinic, Sahlgrenska sjukhuset Göteborg. It can, however, also be utilized for other types of analog recordings, e.g. mass spectra.

### INTRODUCTION

In experimental research and clinical work a large amount of data is often collected which later on is to be treated and analysed. Typical examples are registrations of EEG and ECG and nystagmograms. For this purpose the computer has been put more and more to use. It is particularly desirable that the primary data can be made available to the computer without time-consuming manual operations. The actual measurements can first be recorded on magnetic tape in analog form and then analysed by the computer after sampling and conversion of the analog signals to series of digital numbers.

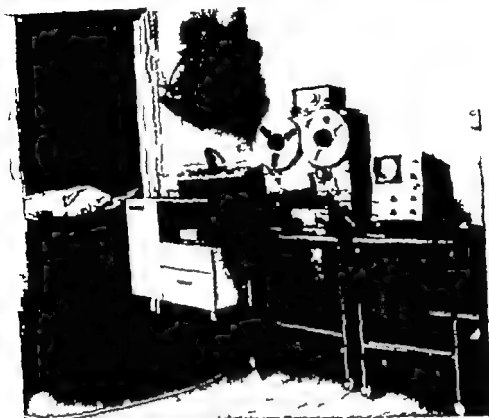


Fig. 1 Equipment for nystagmus test

Such an input of analog data from magnetic tape has been carried out in various laboratories. In this paper a procedure will be described which represents a general and flexible system for different types of analog data. This is illustrated by a description of an automatic analysis of nystagmograms.

#### METHODS

- 1 Registration of nystagmus using Mingograf and recording on magnetic tape
- 2 Interface of the magnetic tape to the computer
- 3 Program system.

##### 1 Registration of Nystagmus

The Mingograf 81 (D.C. Amplifier 8 channels recorder) (Fig. 1) is used for registering and transmitting the response from the patient to the magnetic tape recorder (Ampex SP 300 7 ch.) It is also used for recording control pulses from a signal generator producing a tone of 300 Hz fre-

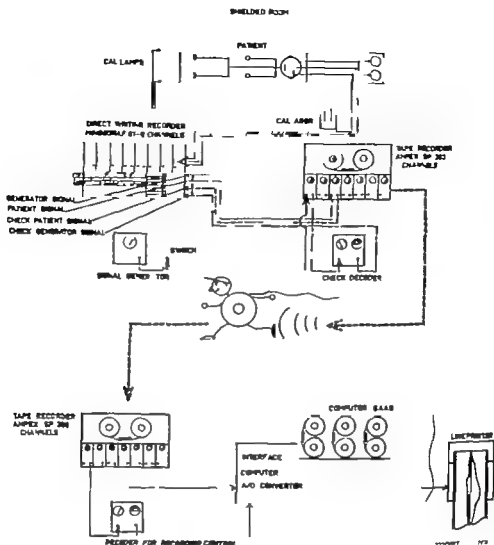


FIG 2. Recording and processing equipment for nystagmus test

quency (Fig 2) This tone is later decoded to a single pulse Every single nystagmus registration is then marked between two distinct pulses, a start and a stop pulse which determine where the computer analysis begins and stops All disturbing factors that are not of the same wave length and amplitude as the control signal are thereby eliminated In its present form the nystagmus test contains 9 different phases of measurement A block diagram of the procedure is given in Fig 3

**Method of calibration for tape recording** In order to get a uniform calibration of the signals from the patient with regard to duration and amplitude we have constructed a calibration unit that consists of a rotating contact disc which gives signals of 2 or 4 seconds duration for 30 seconds. The amplitude of the calibration is recorded so that a horizontal movement of the eyes of the patient with a deviation of 10 degrees gives a pulse of 10-mm height on the Mingograf curve

The advantage of this system of calibration is that it gives uniformity to computer analysis of different patient recordings

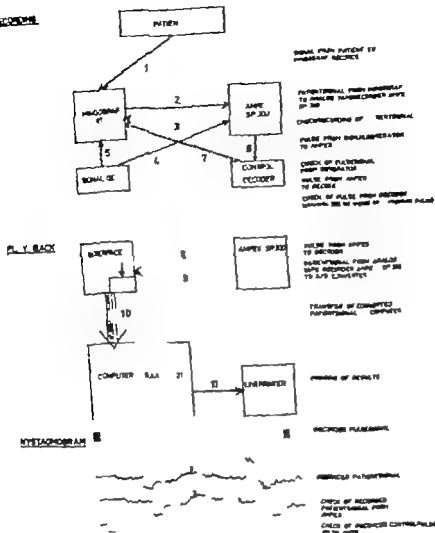


FIG. 2. Processing of vstagn test.

## 2 Interface of the Magnetic Tape to the Computer

The machine used is the Swedish Dataasab D21 computer (Fig. 4). It is a binary fixed-point single-address machine with 24-bit word (cycle time 4.8  $\mu$ s) using magnetic tape as backing memory. This has been supplied with a fast input channel for analog information initially for use with an automatic computer controlled film scanner (Abrahamsson, 1966).

A block diagram of the tape recorder interface to the computer is given in Fig. 5. The signal from the analog tape (1) is amplified (2) and fed to the analog-digital converter (3) which gives 11 bits in 50  $\mu$ s. Conversions are caused by pulses from the clock pulse generator (4). The latter has a variable frequency so that the sampling rate can be adjusted to suit the



FIG. 4 Computer Datagrab D21

experimental conditions. The clear command signal from the converter goes to the transfer control (5) which gives a signal to open the gate (6) if the two other input lines are set to open. The transfer of the digital number in the converter output register to the computer core memory works on a cycle stealing basis and does not interfere with the program being obeyed by the computer.

In order to control the input procedure program interrupts are obtained through a decoder (8) for each of the control signals recorded on a parallel channel on the tape. These pulses change the state of the transfer control

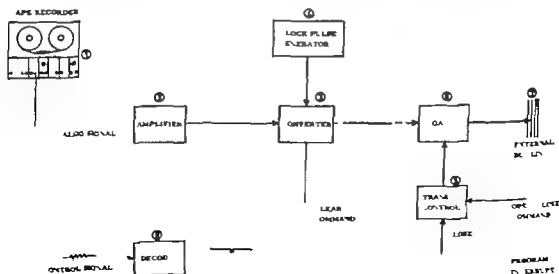


FIG. 5 Interface to computer



FIG. 6 Printout of 1 gm analysis.

setting one input line to close. No transfers to the computer are thus possible during a program interrupt. The third input line to (5) is controlled by a special position in a computer register which is set by program. This offers full program control over the data transfer.

### 3 Program System

The following programs have been written for the analysis of nystagmographic data. The first two (READ and FILTER) are not specific for this particular application but can be used for any type of input data. They are written in a assembler language (Dac 1 autocode) whereas the analysis programs are coded in Algol.

A. *READ* The user specifies sampling rate, tape speed and the control signal program applicable to the tape data. The latter can either be different from the whole tape or be set to repeat itself in order to handle a number of similar experiments along the tape, i.e. series of patient data. It is thus possible not only to search for a particular recording on the tape but also to transfer any selected part of it to computer. The transferred data are stored on computer magnetic tape for further treatment.

B. *FILTER* The analog signal is often sampled at relatively high frequency and then filtered numerically to give a smoothed signal. The program allows the user to select a number of numerical filters for his problem. In addition the program accepts as input various descriptions of the digitized record, (e.g. patient data). All data are then stored on magnetic tape in a form required by the Datasah Algol/Genius programming system.

C. *VISTCOMP* This is the specific program for analysis of nystagmus data recorded and edited by the previous programs. It calculates





### *Evaluation of the Computer Results*

The computer results of different types of nystagmograms are being analysed to find adequate criteria for a useful clinical system. About 200 nystagmograms on magnetic tape have been collected. We have used recordings from the routine clientele. A few typical cases with various vestibular disturbances have been selected for detailed study. We have found a good correspondence between the computer results and the direct reading from the nystagmograph curves in the conventional way. These preliminary results indicate that the computer analysis will give more information concerning details in the nystagmus reactions than the conventional analysis. More definite conclusions, however, can be drawn when a large amount of data has been analysed and treated statistically.

### DISCUSSION

There are certain methodological points of importance for the solution of the problem that we wish to emphasize.

1. The control pulse gave considerable trouble before we arrived at the solution described. This pulse is of great importance for administration of the input procedure. Our solution has made it possible to obtain a reliable operating system by excluding disturbing start and stop pulses.

2. Voluntary eye-movements of excessive amplitude, which are very common in the initial period after calorisation, can be excluded from analysis. Other solitary eye movements of large amplitude during the reaction can also be excluded by an idealisation of the curve using the computer. Even very small spikes on the slow phase of the curve are of interest as they give a higher differential value than the average inclination of the curve. We have chosen an amplitude of 3 degrees as minimum value.

3. In many cases it is necessary that the direction of nystagmus could be distinguished by the computer. This problem has been solved in principle.

In the near future we intend to use this computer analysis for the study of vestibular function with other stimuli such as rotation and pendulating (Greiner). Preliminary experiments are in progress.

### RÉSUMÉ

Des résultats électro-nyctagmographiques obtenus par examen calorique de routine sont enregistrés de façon analogue sur bandes magnétiques, puis transformés et analysés par un ordinateur digital. Les bandes sont marquées par impulsions de contrôle et il est possible de retrouver les résultats d'un malade particulier. Le programme actuel utilise la fréquence, l'amplitude, la réponse différenciée linéaire et pour évaluer la possibilité d'utiliser routinemièrement cette méthode.

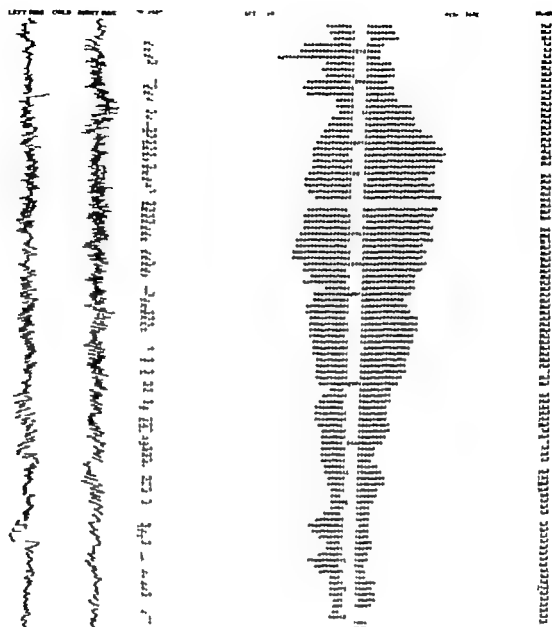


FIG 7 Results of nystagmus analysis. Left: Direct recording; Right: Differentiated response.

- Differentiated response under correction for spontaneous nystagmus.
- Total amplitude
- Total number of beats within different phases of the recording
- Duration of each phase
- Occurrence in time of maximum response and its size
- Maximum frequency

**D NYSTPRINT** The response characteristics evaluated by NYSTCOMP are printed numerically. The differentiated response can also be displayed graphically on the line printer. Examples of the printout are given in Figs 0 and 1.

## STROBOSCOPIC LAMINAGRAPHY OF THE LARYNX DURING PHONATION

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A significant advance in the use of radiological instruments for the study of human physiology was made in 1943, when Griesman reported that he used coronal laminagrams to observe the human vocal folds during phonation. He presented and discussed laminagrams made of several singers while they were producing various vocal pitches. Griesman's work showed that the laminographic approach was useful in the study of laryngeal phenomena. However, the first quantitative studies undertaken using conventional laminography techniques were by Hollien & Curtis in 1954. In these studies, measurements of the cross-sectional area and thickness of the vocal folds were related to changes in fundamental frequency of phonation. Figure 1 is an example of a normal section laminagram showing the vocal folds during phonation. While laminography represents an advance over older techniques of conventional radiological techniques, it suffers from several limitations. First, the image portrayed by this method is a composite built up during many vibratory cycles of the folds. The effect is one of blurring of the rapidly vibrating cord edges, which may be effected by such dynamic factors as amplitude of motion, duration of closed phase, etc. Thus, while investigators can measure the composite image to derive cross-sectional area and thickness, enough differential variation may occur in the experimental procedure to cast doubt upon the validity of the result.

To overcome some of these obstacles and others which are related to such techniques as ultra-high-speed photography, a stroboscopic laminagraph has been developed which provides a series of laminographic X-ray photographs. The photographs display a coronal cross-section of the vocal folds at ten separate phases of the laryngeal cycle. The system has the advantage of allowing most subjects to be used, and requires no modification of the phonational mechanism such as the introduction of a laryngeal mirror or topical anesthesia.

The system still retains some of the limitations of conventional laminography. That is, the resultant picture is still a composite image of numerous cycles, although the image is taken in the same phase. In addition, only one plane along the antero-posterior extent of the vocal folds can be visualized during any one experimental condition. The major advantage, however, is that one may obtain a coronal section of the vocal cords during a dynamic phonatory act.

## ZUSAMMENFASSUNG

Elektronystagmographische Befunde welche auf übliche Weise durch kalorische Reizung erhalten wurden werden in Analogform auf Magnetband aufgenommen dann in Digitalwerten vorgewandelt und zur Analyse direkt in einen Digitalcomputer gegeben. Auf dem Analogband befinden sich Kontrollsignale welche es erlauben die Sonderbefunde der einzelnen Patienten rasch zu finden. Unser Programm benutzt Frequenz, Amplitude Differentialanalyse Dauer usw. mit dem Ziel, die mögliche klinische Auswertung des automatisierten Verfahrens abzugrenzen.

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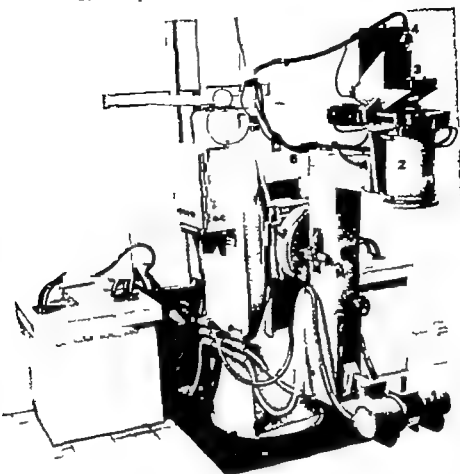


FIG. 2. The laminagraphic drive, X-ray and optical system of STROL. The components pictured are (1) X-ray tube (2) image intensifier tube; (3) 25 mm camera; (4) TV camera (5) the drive, and (6) yoke stand.

lowing the training periods, subject matched a tone presented to them by earphone. They and the experimenters monitored the vocal performance by a beat meter. While the subjects did not maintain a completely steady tone, the variation around the mean frequency was somewhat less than  $\pm 2$  Hz.

The intensity of the vocal output was maintained by first asking subjects to produce the selected pitch at a comfortable level. The microphone gain was then adjusted so that if the subject dropped his intensity by as much as three dB, his voice could not trigger the X-ray mechanism. Excessive vocal output was monitored by two persons during each run, who disqualified a subject on a particular run if he exceeded the intended level by three dB.

The resultant ten pictures in each experimental condition were examined



Fig. 1. A photograph of a normal section of the vocal folds in coronal cross-section.

Figure 2 is a photograph of the STROL mechanical system; the accompanying legend identifies those individual components that can be seen externally. It should be noted that this apparatus has been arranged specifically for photography with much of the associated equipment removed. During actual operation the supporting components and a table for the subject are included. Figure 3 provides the STROL schematics; each of the components is identified on the diagram.

The preliminary data reported here utilized four male subjects phonating at four separate fundamental frequencies of 98, 124, 153, and 196 Hz, which are four semitones apart and cover a full octave from G<sub>1</sub> to G<sub>2</sub>.

The subjects' vocal range was determined in a screening session by having them match complex tones on an ascending and a descending scale. The total range of the subjects used was an average of 72 semitones. The widest range was 39 semitones while the most restricted was 27.

The subjects were familiarized with the equipment and instructed in the procedure for the experimental session during a brief training period. Fol-

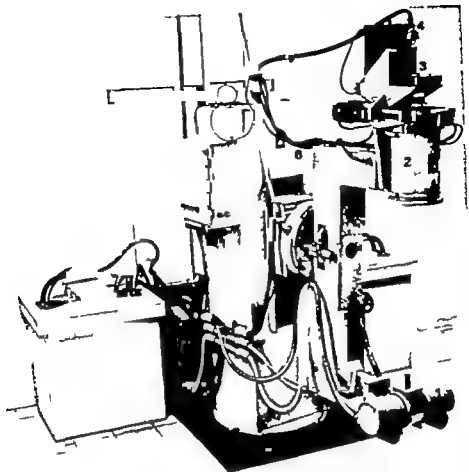


Fig. 2 The laminographic drive and optical system of STROL. The components pictured are: (1) X-ray tube; (2) image intensifier tube; (3) 25 mm camera; (4) TV camera; (5) motor drive; (6) yoke stand.

low in the training periods, subjects matched a tone presented to them by earphone. They and the experimenters monitored the vocal performance by a beat meter. While the subjects did not maintain a completely steady tone throughout the run, the mean frequency was somewhat less than 2 Hz.

The intensity of the vocal output was maintained by first asking subjects to produce the selected pitch at a comfortable level. The microphone gain was then adjusted so that if the subject dropped his intensity by as much as three dB, his voice could not trigger the X-ray mechanism. Excessive vocal output was monitored by two persons during each run who disqualified a subject on a particular run if he exceeded the intended level by three dB.

The resultant ten pictures on each experimental condition were examined



and the ones showing closure were subjected to cross sectional area and thickness measurements. The procedures for measuring the vocal fold pictures were the same as those which Hollien & Curtis had employed earlier. Figure 4 shows a highly stylized drawing of the way in which the folds were outlined for measurement. The lines AB of the airway margins and

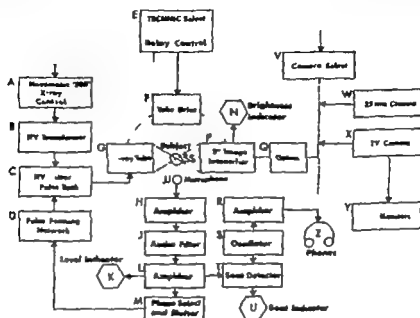


Fig. 3 Block diagram of STROL.



Fig. 4

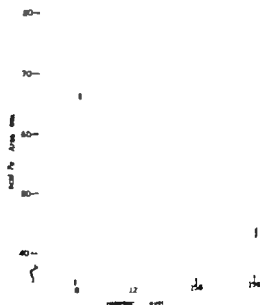


Fig. 3

FIG. 4 A tracing of a filmograph of the local field showing the reference lines used in obtaining coronal cross sections and the lines measuring it.

FIG. 5. Scatter plot of cross-correlation coefficients  $\rho_{xy}$  at each of the frequencies.

all other relevant lines were independently drawn on separate transparent sheets by two persons. In case of disagreement, redefinition by the two experimenters and measurements by a third judge were used. Through a long series of photographic trial and error the prints used for measurement were clear enough that disagreement among the experimenters was rare.

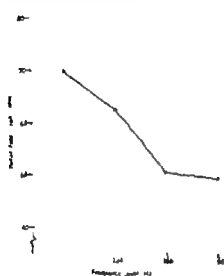


Fig. 6.

FIG. 6. Area of the area measurement for the four subjects.

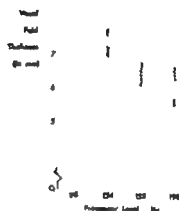


Fig. 7.

FIG. 7. Relation in vocal fold thickness to action of fundamental frequency.



FIG. 8. Mean of the vocal fold thickness measurements.

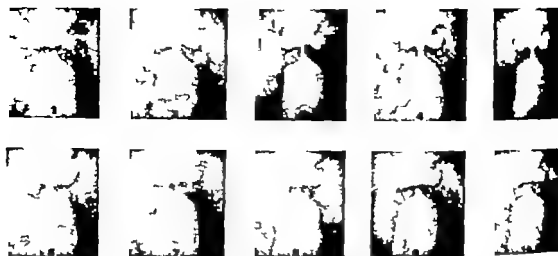


FIG. 6. An illustrative series of stroboscopic laminograms showing the vibratory action of the vocal folds in coronal cross-section.

After the basic outlines of the folds were completed they were measured for cross sectional area by polar planimeter. Planimeter measurements were made by two separate judges. The enlargement factor of the prints was determined and the planimeter measures were adjusted accordingly to give final measures in millimeters.

The results of the cross sectional area measures are displayed in Figure 5. The eight data points at each frequency level represent area measures of the four subjects' two vocal folds. While the wide range of area measurements for any one frequency level is apparent, the general trend is for vocal fold cross sectional area to be inversely related to increases in fundamental frequency.

Figure 6 portrays an average of all four subjects' area measurements at the four frequencies. The apparent flattening out of the curve between the two highest frequency levels might be attributed to an artifact of the small group data, or that the subjects were phonating at a relatively high frequency probably at the upper end of their modal register.

Figure 7 portrays changes in vocal fold thickness at the four frequency levels used. You will note several more data points per frequency level than on the cross-sectional area measurements. This is due to the fact that we added several subjects on whom we only had one or two frequency conditions. A total of eight subjects' data is shown with several re-test conditions included. The purpose of adding the extra subjects is to indicate maximal differences among the subjects. The trend is obvious that vocal fold thickness is inversely related to increases in frequency levels.

Figure 8 is an average of these data, and illustrates the point again. The present results, then, are presented as substantiating data for Holtien & Curtis' previous conclusions using conventional laminagraphic techniques. A much larger study is now under way which includes very precise control of frequency and intensity characteristics. In the new study each subject

is required to produce frequency and intensity levels based on percentages of his own vocal ranges, rather than absolute levels used here. With more sophisticated techniques now employed, it is anticipated that the intra-subject variability may be reduced, and more closely related relationships defined.

It is not possible to provide motion pictures in a paper such as this one however. Figure 9 is a set of ten stroboscopic laminagrams of a human subject. These films are taken directly from our work prints and, by means of animation techniques, constitute the basis of our motion pictures. In these photographs, the subject is phonating at 124 Hz and at a relatively soft vocal intensity. Even from photographs such as these it may be noted that only the superior medial borders of the vocal folds approximate closed time constitutes 20-30% of the duty cycle. This finding is consistent with previously reported laryngeal photography data.

In summary, stroboscopic laminagraphy is proving to be a useful research tool in the study of laryngeal function.

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#### DISCUSSION

P. H. H. Lange: We appreciate Dr. Coleman bringing this work to the Colloquium and wish him to take our greetings to Dr. Hollen and Dr. Moore. This important research tool adds a new dimension to the studies of phonation which Dr. Moore and others have already made in this field. I should like to ask Dr. Coleman if other phonologic functions of the larynx such as cough and deglutition, have been similarly studied. Also I hope he will tell us the approximate radiation exposure the larynx of the patient receives during such study.

R. F. Coleman (Reply) to M. Holling: Thank you for your comments, Mr. Hollinger. In reply to your first question I would review the fact that STROL operates on a stroboscopic principle which in turn depends upon a relatively steady-state vocal source. In order to achieve a series of phased pictures, we must use approximately ten seconds of phonation from the subject. Since a cough or a flowing action is essentially a transitory phenomenon, we are unable to use STROL for such studies. We can of course observe such function in real time without stroboscopic laminagraphy. Concerning the radiation exposure of the subject's larynx, I would say that this is quite variable due to different pulse rates, related to the subject's fundamental frequency. The maximum exposure rates, however, are well within conservative limits set by the Radiation Control Committee of the University of Florida.

## EINE FUNKTIONELLE STUDIE ÜBER DIE PNEUMATISATION DES SCHLÄFENBEINS

A MEYER ZUM GOTTESBERGE, M.D

*Dusseldorf Deutschland*

Die enorm entwickelte Pneumatisation des Schläfenbeins bei den Pongiden insbes. beim Gorilla läßt eine spezifische Funktion vermuten wie sie bei den Walen bereits nachgewiesen wurde die Isolation des Innenohres gegen Knochenschall Modellversuche zeigen daß pneumatisches Gewebe eine schalldämpfende Wirkung erst oberhalb 1000 Hz entfaltet Eine mehrschichtige der Schädeldecke ähnliche Membran zeigt eine schalldämpfende Wirkung im unteren und oberen Frequenzbereich, aber eine ausgeprägte Eigenresonanz Die günstigste schalldämmende Wirkung ergibt die Koppelung der Membran mit pneumatischem Gewebe Die schalldämmende Wirkung erstreckt sich auf den ganzen Frequenzbereich mit Bevorzugung der oberen Frequenzen Die Eigenresonanz der Membran wird dabei deutlich gedämpft.

Ob die Pneumatisation des Schläfenbeins eine funktionelle Bedeutung hat und ob sie einer solchen Betrachtung wert ist, mag gewisse Zweifel erregen Solche Zweifel verstummen aber wenn man die Pneumatisation in ihrer fortgeschrittensten Entwicklung betrachtet

Die höchste Entwicklungsstufe erreicht die Pneumatisation des Schläfenbeines bei den Menschenaffen insbes. beim Gorilla Die eindrucksvollen Bilder die Sie im folgenden sehen und überhaupt die Anregungen zu unseren Untersuchungen verdanke ich dem Röntgenologen Professor Bergerhoff in Köln Die untersuchten Schädel stammen aus der von Professor Velt angelegten Sammlung des Anatomischen Institutes in Köln Für alle anatomischen und röntgenologischen Einzelheiten muß ich auf die ausführliche Arbeit die Herr Bergerhoff in Kürze veröffentlichen wird, verweisen.

Wenn man die ausgedehnte Pneumatisation des Felsenbeines des Gorillaschädels betrachtet, so kann man sich schwer dem zwingenden Eindruck entziehen daß hier der Pneumatisation eine besondere Aufgabe zugewiesen wurde Nach allen Richtungen hin ist das Innenohr durch eine mehrere Zentimeter dicke pneumatische Zellschicht von seiner Umgebung isoliert Diese Zellschichten treten nach lateral wie die Röntgenaufnahmen zeigen weit aus dem Schädel heraus, um die am Schtettel ansetzende mächtige Kaumuskulatur zu unterpolstern Das Schläfenbein selbst ist mit der Schädelbasis nicht knöchern sondern nur bindegewebig verbunden Bei den übrigen Menschenaffen (Pongidae) dem Pongo (Orang Utan) Pan (Schimpanse) Hylobates (Gibbon) ist die Pneumatisation des Schlä



Abb. 1. Gorillaschädel, anterior-posteriore &amp; faciale

Abb. 2. Gorillaschädel, seitliche &amp; faciale

f beins ähnlich strukturiert, wenn auch in wesentlich geringerem Ausmaße als beim Gorilla.

Bei allen diesen Arten befinden sich das Innenohr und die Paukenhöhle im Inneren eines ausgedehnten pneumatischen Zellsystems, welches ist die Aufgabe dieses Zellmantels in den gegebenen Möglichkeiten, die sich leicht ausschließen. Schutz gegen mechanische, akustische oder thermische Einwirkung — erscheint die akustische Isolations als die weitestwichtigste.

Eines der hervorragendsten Bauprinzipien des Gehörganges ist die Herabsetzung des Knochen-schalles. Die außerordentlich niedrige Schwelle für Luftschall kann überhaupt nur dann wirksam werden, wenn der Knochen-schall stark gedämpft wird. Beim Kauen, Schlucken, bei der Stimmgebung beim Gehen usw. entstehen mannigfache Körpergeräusche die als Knochen-schall werden und verdeckenden Charakter haben.

Wenn in der Hörschwelle diese Geräusche sind, läßt sich zeigen wenn die Knochenleitung durch Verschluss des äußeren Gehörganges um ca. 10 Db erhöht wird. Békésy konnte unter diesen Bedingungen normale Gehörswegen hören wie man sich leicht selbst überzeugen kann. Nach eigenen Beobachtungen läßt sich durch Verschluss des Gehörganges die Pulsation der Carotis interna wahrnehmen. Die Schwelle mancher körpereigener Geräusche liegt offen heilich nur wenige Db unter der normalen Hörschwelle in Luftleitung.

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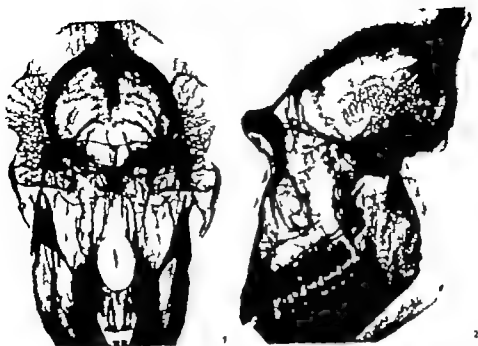


Abb. 1. Gorillaschädel, anterior-posteriore Ansicht

Abb. 2. Gorillaschädel, seitliche Ansicht

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Bei allen diesen Arten befinden sich das Innenohr und die Paukenhöhle im Inneren eines ausgedehnten pneumatischen Zellsystems. Welches ist die Aufgabe dieses Zellsystems? In den gegebenen Möglichkeiten, die sich nicht an schließen Schutz gegen mechanische akustische oder thermische Einwirkung — erscheint die akustische Isolation als die weitaus wichtigste.

Eines der hervorragendsten Bauprinzipien des Gehörganges ist die Herabsetzung des Knochenfalls. Die außerordentlich niedrige Schwelle für Luftschall kann überhaupt nur dann wirksam werden, wenn der Knochenfall stark gedämpft wird. Beim Kauen, Schlucken, bei der Stimmgebung, beim Gehen usw. entstehen mannigfache Körpergeräusche die als Knochenfall stören und erdrückenden Charakter haben.

Wie nahe der Hörschwelle diese Geräusche sind, läßt sich zeigen, wenn die Knochenleitung durch Verschluss des äußeren Gehörganges um ca. 10 Db erhöht wird. Békésy konnte unter diesen Bedingungen normale Gehbewegungen hören, wie man sich leicht selbst überzeugen kann. Nach eigenen Beobachtungen läßt sich durch Verschluss des Gehörganges die Pulsation der Carotid interna wahrnehmen. Die Schwelle mancher körpereigener Geräusche liegt offenbar lediglich nur wenig Db unter der normalen Hörschwelle in Luftleitung.



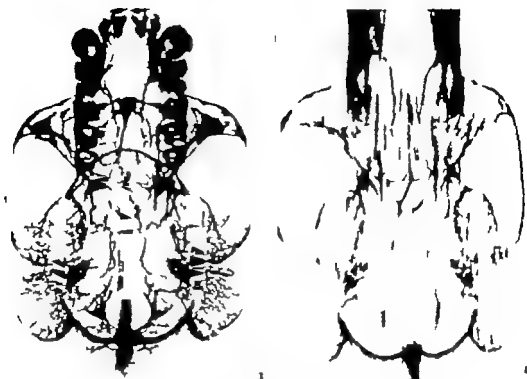


Abb. 3 Gorillaschdel, Baßaufnahme

Abb. 4 Gorillaschdel, Tomogramm horis ut 1 10 cm

Eine interessante Studie hat Békésy dem Prinzip des „minimalen knochenschalls“ gewidmet. Er schreibt: „Wenn man die beste Position für das Mittelohr im Schädel suchen will, so ist eine Lage so tief wie möglich im Schädel die beste, um den größten Schutz zu erhalten.“ Békésy zeigt, wie bei Biegunsschwingungen einer relativ dicken Knochenschale die äußere Hälfte gedehnt, die innere gepreßt wird, während in der Mitte zwischen beiden eine Indifferenzzone nur Scherkräften ausgesetzt ist. Infolgedessen ist bei Lebewesen mit dicken Schädelsknochen (Mensch, Ochs) eine Lagerung des Mittelohres in der Mitte des Knochens zum Schutz gegen Knochenschall am günstigsten. Bei kleineren Tieren, deren Schädelsknochen zu dünn sind (Hunde, Katzen, Mäuse), tritt an die Stelle einer dicken Knochenschale der lufthaltige Hohlraum der Bulla, in den z. B. beim Meerschweinchen die Cochlea weit hineinragt. Es läßt sich allerdings einwenden, daß die anatomischen Verhältnisse beim Menschen wesentlich komplizierter als in dem von Békésy angegebenen Modell sind.

Es ist nun die Frage, welche Vorteile die Einbettung des Mittel- und Innenohres in pneumatisches Material gegenüber der in festen Knochen hat. Hierfür können folgende Gründe maßgebend sein. Das pneumatische Material ist im spezifischen Gewicht leichter. Da die lufthaltigen Zellen mit der Paukenhöhle in Verbindung stehen, dienen sie gleichzeitig als Luftraum hinter dem Trommelfell und gewährleisten die Beweglichkeit des Trommelfelles (Békésy 1960). Sie erleichtern aus dem gleichen Grunde

Prüfgerät für kystische  
WiderständeMaß der Wirkung auf 1 cm  
Außen- und InnenflächeDurchfall durch 1 cm auf 1 cm  
Innenfläche

Eingeleitet: Schwingungen

Kunststoffkapsel 1/2 cm  
BreiteInjektions-Blasenmaterial  
verschiedenen Art: GewebeAnzahl der Proben oder  
SchichtenInjektionsmaterial  
verschiedenen Art: GewebeMessung der  
Schwingung

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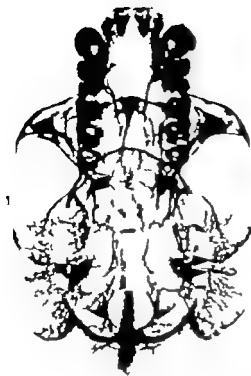
Messung der Schwingung

Abb. 5. Prüfgerät für akustische Widerstände

die Tubenfunktion. Letztlich hat poröses Material selbst schallabsorbierende Eigenschaften. Mit der letzteren Frage in welchem Umfange auch pneumatischen Zellen diese Eigenschaft zukommt haben wir uns experimentell etwas näher beschäftigt.

Für Messungen der akustischen Eigenschaften pneumatischen Gewebes standen zwei Wege zur Verfügung, die Untersuchungen am lebenden oder toten Schädel oder Modellversuche an künstlich nachgebildetem Material, d. h. an Blasenkunststoff. Die Möglichkeiten der ersten Methode wurden von uns eingehend erwogen da uns aus der Sammlung des Anatomischen Institutes der Universität Köln mehrere sehr gut präparierte Schädel großer Menschaffen, u. a. des Gorilla zur Verfügung standen. Es verstand sich aber von selbst daß die wertvollen Sammlungstücke auf keinen Fall beschädigt werden durften. So war es leider ausgeschlossen, etwa in die Paukenhöhle oder das Innenohr ein Mikrofon einzubauen. Da außerdem die akustischen Bedingungen infolge des anatomischen Baues des Felsenbeines sehr unübersichtlich sind, entschlossen wir uns zu Modellversuchen, bei denen die akustischen Verhältnisse einwandfrei überschaubar sind. Der Einwand, daß das Modellgewebe vom Körpergewebe allzu verschieden sei — ein Argument, das sehr häufig von Medizinern gegen Modellversuche vorgebracht wird — wiegt nicht allzu schwer. Es zeigt sich vielmehr daß es mehr auf den strukturellen Aufbau des Gewebes als auf seine physikalisch-chemische Beschaffenheit ankommt.

Zur Messung des akustischen Widerstandes des offenporigen Blasenkunststoffes wurde ein Prüfgerät benutzt, das in Abb. 5 dargestellt ist. In der Versuchsanordnung befindet sich links der Ansatz für die Schallquelle rechts ist das Meßmikrofon angebracht. In der Mitte kann poröser Kunst-



3



4

Abb 3 Gorilla chiddei B Kaufmann

Abb 4 Gorilla chiddei Tomogramm horizontal 10 cm

Eine interessante Studie hat Békésy dem Prinzip des minimalen Knochenschalls gewidmet. Er schreibt: „Wenn man die beste Position für das Mittelohr im Schädel suchen will, so ist eine Lage so tief wie möglich im Schädel die beste, um den größten Schutz zu erhalten.“ Békésy zeigt, wie bei Biegungsschwingungen einer relativ dicken Knochenschale die äußere Hälfte gedehnt, die innere gepreßt wird, während in der Mitte zwischen beiden eine Indifferenzzone nur Scherkräften ausgesetzt ist. In folgedessen ist bei Lebewesen mit dicken Schädelknochen (Mensch, Ochse) eine Lagerung des Mittelohres in der Mitte des Knochens zum Schutz gegen Knochenschall am günstigsten. Bei kleineren Tieren, deren Schädelwandungen zu dünn sind (Hunde, Katzen, Mäuse), tritt an die Stelle einer dicken Knochenschale der lufthaltige Hohlraum der Bulla, in den z. B. beim Meerschweinchen die Cochlea weit hineinragt. Es läßt sich allerdings einwenden, daß die anatomischen Verhältnisse beim Menschen wesentlich komplizierter als in dem von Békésy angegebenen Modell sind.

Es ist nun die Frage, welche Vorteile die Einbettung des Mittel- und Innenohres in pneumatisches Material gegenüber der in festen Knochen hat. Hierfür können folgende Gründe maßgebend sein. Das pneumatische Material ist im spezifischen Gewicht leichter. Da die lufthaltigen Zellen mit der Paukenhöhle in Verbindung stehen, dienen sie gleichzeitig als Luftraum hinter dem Trommelfell und gewährleisten die Beweglichkeit des Trommelfelles (Békésy 1960). Sie erleichtern aus dem gleichen Grunde

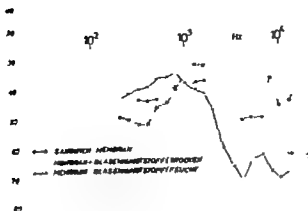


Abb. 7 Schalldämmung d. reh Membran d. poröser Kunststoff (T rüffler)

50 Db. Die schalldämmende Wirkung ist, wenn die Substanz befeuchtet aber wieder ausgepreßt wird, so daß die Poren lufttchtig sind, kaum meßbar größer. Sie ist deutlich größer wenn die Poren Wasser enthalten.

Eine schalldämmende Wirkung auch bei tieferen Frequenzen (200–1000 Hz) wird erzielt, wenn dem porösen Kunststoff eine mehrschichtige Membran (Sandwich Membran) die in ihrer Dicke und Struktur etwa der Schädeldecke entspricht, vorgeschaltet wird. In diesem Falle beträgt die Schalldämmung bei 200–1000 Hz 40–45 Db und steigt bis auf 60–70 Db bei 10 000 Hz. Die Eigenresonanz der Membran bei 1000 Hz (Schädel 1800 Hz) wird durch den porösen Kunststoff deutlich gedämpft (Abb. 7).

Die Schalldämmung im porösen Material kommt dadurch zustande daß die Luftteilchen in den Poren durch den einfallenden Schall zum Schwingen erregt werden und daß durch Reibung Schallenergie in Wärme verwandelt wird. Die Schallabsorption poröser Stoffe ist stark frequenzabhängig und bei tiefen Frequenzen nur gering. Zur Schallabsorption tiefer Frequenzen eignen sich Materialien, die zu Biegeschwingungen fähig sind (Trendelenburg, 1950).

Schon frühere Untersucher haben sich mit der Frage des Schallschutzes durch das Luftströmungssystem der Pneumatisation beschäftigt. Dabei wurde jedoch bisher die Möglichkeit einer Innenohrschädigung gedacht. Wittmann (1934) der die heutige Theorie der Lärmschädigung durch Knochenleitung kritisch verurteilte, vermutete eine Verstärkung der Knochenleitung im pneumatisationsgehemmten Warzenfortsatz. Link & Handl (1955) haben in der Pneumatisation einen Schutz gegen Lärmschwerhörigkeit gesehen. Von dieser Auffassung unterscheidet sich unsere in einem wesentlichen Punkte. Die akustische Isolierung des Innen- und Mittelohres dient nach dem Prinzip der minimalen Knochenleitung der Aufgabe die Luftleitung gegen Verdeckung durch Knochenleitung, und zwar besonders im Niveau der Hörschwelle zu sichern. Die Pneumatisation könnte außerdem die Eigenresonanz des Schädels dämpfen („Entdröhnungseffekt“).

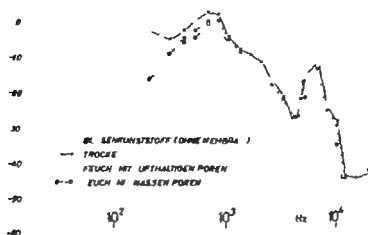


Abb. 6 Schalldämmung durch porösen Kunststoffs (Terzfilter)

stoff mit oder ohne Membran eingeklebt werden. Ein akustischer Nebenschluß ist bei dieser Versuchsanordnung ausgeschlossen, da die Umwegdämmung stets größer als die Meßdämmung ist. Es wurden zwei verschiedene Kunststoffe mit folgenden Eigenschaften benutzt:

	2 mittel	10 mittel
Raumgewicht—Density kg/m	45–50	40–45
Zugfestigkeit—Tensile strength Kp/cm <sup>2</sup>	0,5	2,5
Bruchdehnung—Elongation of break %	90	210
Stauchbarkeit bei 40 (ohne Vorbehandlung) Load carrying capacity p/cm	97	219
Druckspannung—Compressive stress Stauchung, p/cm	90 111	80 210

Während das Raumgewicht, welches das Verhältnis der Poren zur festen Substanz wiedergibt, in beiden Fällen das gleiche ist, übertrifft der zweite Stoff hinsichtlich Zugfestigkeit, Bruchdehnung, Stauchhärte und Druckspannung den ersten bei weitem. Bei den Messungen ergab sich wie vorweg bemerkt werden kann, zwischen beiden Stoffen kein Unterschied. Die zuletzt genannten Eigenschaften sind daher für die Schalldämmung ohne wesentlichen Einfluß. Inwieweit die Größe der Poren und das Raumgewicht von Bedeutung sind, soll noch eingehender untersucht werden. So könnte vielleicht die beim Menschen sehr variable Zellengröße, die nach außen auffällig zunimmt, von Bedeutung sein. Wie aus Abb. 6 hervorgeht, tritt eine schalldämmende Wirkung bei der von uns verwandten pneumatischen porösen Substanz erst ab 1000 Hz ein. Sie erreicht erst oberhalb 10 000 Hz

d'une fonction particulière. Comme cela a été démontré chez la batte, c'est à dire d'isoler l'oreille interne de la conduction osseuse. Les recherches faites, à l'aide d'un modèle ont montré qu'il le tissu pneumatique provoque l'effet d'amortissement son ne seulement au-dessus de 1000 Hz. La membrane constituée de plusieurs couches semblables à celles du crin montre un effet d'amortissement dans une des fréquences basses et hautes. Mais avec une résonance nette l'effet d'amortissement du son le plus favorable est obtenu en couplant la membrane avec du tissu pneumatique. Il couvre un son comportant toutes les fréquences avec une préférence pour les fréquences élevées. Aussi la résonance de la membrane est remarquablement réduite.

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Bei den Walen finden sich in analoger Weise große, das Petrosium umgebende Räume die von Luftschaum erfüllt sind. Diese Räume dienen, wie wohl heute allgemein als sicher angenommen wird, der akustischen Isolierung gegen Knochenschall. Wale verfügen über ein hochentwickeltes Gehörorgan mit der Fähigkeit zu binauraler Lokalisation. Eine binaurale Lokalisation für Wasserschall setzt eine Isolierung der Felsenbeine gegen den Schädelknochen voraus. Der enge Gehörgang der Wale leitet die Druckwelle des Wassers selektiv zum Trommelfell, das wie der ganze schallleitende Apparat der Schallhärte des Wassers angepaßt ist (Fraser & Purves 1960, Reysenbach de Haan 1957). Auf diese höchst sinnreiche Weise wird der Wasserschall den gegeneinander isolierten Labyrinthenzugeführt und eine binaurale Lokalisation ermöglicht.

Bei Landlebewesen, deren Ohr Luftschall aufnimmt, ist die akustische Isolierung des Hörorgans gegen Knochenschall nicht in solchem Maße zwingend lebensnotwendig wie bei den im Wasser lebenden und Wasserschall aufnehmenden Cetacea. Die Pneumatisation des Schläfenbeins entwickelt sich nur bei den auf höchster Entwicklungsstufe stehenden Primaten zur Vollkommenheit und ist beim Menschen bereits wieder in Rückbildung begriffen. Nach der heute vorherrschenden Auffassung dürfte die Pneumatisation primär hereditär bedingt sein. Ihre extreme Variabilität ist, wie schon Darwin im Prinzip erkannte, ein sicheres Zeichen, daß die Pneumatisation als Erbfaktor beim Menschen keiner Selektion mehr unterliegt und funktionell relativ bedeutungslos geworden ist.

Mein herzlicher Dank gilt Professor Dr. Bergerhoff, Köln, für die Anregungen zu diesen Untersuchungen und die Röntgenbilder, Professor Dr. Velt und Professor Dr. Ortman, am Anatomischen Institut der Universität Köln, für die teilweise Überlassung der Schädelsammlung. Meinen Mitarbeitern Professor Dr.-Ing. Meister und Dipl.-Ing. Ruhrberg für die ausgeführten Messungen.

## SUMMARY

The enormously developed temporal bone-pneumatisation of the pongides, especially of the gorilla, has presumably a specific function as has already been proved with whales. The isolation of the inner ear from bone-conduction Model experiments showed that the pneumatic tissue displays a sound-damping effect only above 1000 Hz. A membrane consisting of several layers, similar to that of the skull, shows a sound-damping effect in the sphere of the medium and upper frequencies, but with pronounced resonance. The most favourable sound-damping effect is achieved by coupling the membrane with pneumatic tissue. It covers the complete sphere of all frequencies, with a preference for the upper frequencies. Thus the resonance of the membrane is remarkably reduced.

## RÉSUMÉ

Le très important développement de la pneumatisation du temporal chez l'anthropoïde en particulier chez le gorille est probablement la conséquence

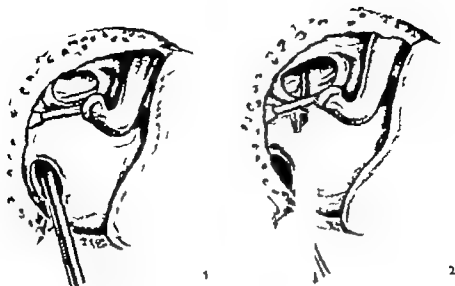


FIG. 1 Round window irradiation.

FIG. 2 Oval window irradiation.

The endoaural surgical approach to the ear windows is the same as for stapes surgery.

#### A Round window irradiation

The round window is seen from an oblique angle and in very few cases its membrane can be seen. In some instances it could appear necessary to drill very gently the anterior border of the round window in order to obtain a better introduction of the tip of the irrigator. The middle ear cavity must be free of blood before applying the irrigator; a drop of physiological solution is put on the round window niche to assure a good transduction of ultrasonic waves into the round window membrane.

After 10-20 seconds a small irritative nystagmus of 1 degree, directed toward the irradiated ear appears. This nystagmus develops on two planes: on the horizontal plane and on the rotatory plane; sometimes vertical nystagmus is also present. In some cases, after 60-90 seconds, the irritative nystagmus attenuates, and a paralytic nystagmus, directed toward the non-irradiated ear of the same entity of the first, appears. Sometimes we noticed that the two nystagmi are contemporaneous.

The patient is discharged as early as 3 or 4 days after the intervention (Fig. 1).

#### B Oval window irradiation

This irradiation presents two advantages:

1. The oval window faces the vestibule and not the tympanic scale and the cochlear duct, which are facing the round window.



## ULTRASONIC SELECTIVE IRRADIATION OF THE EAR WINDOWS, AS A NEW TREATMENT OF VERTIGO AND TINNITUS

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The author presents the first results observed after ultrasonic irradiation at low intensity in a group of patients suffering from Menière's disease and other types of labyrinthosis. (1) Round window irradiation seems to be indicated by cases of severe deafness accompanied by very troublesome tinnitus depending not only on Menière's disease but also on cochlear dropical lesions, sudden deafness of vascular origin. (2) Oval window irradiation seems to be indicated by Menière's disease in which hearing ought to be preserved.

Kossoff (1968) has recently built a thin ultrasonic irradiator designed for irradiation of the round window. He started from the ascertainment that when applied to the membrane of the round window the ultrasonic beam does not pass through bone and can therefore directly reach the membranous labyrinth with an intensity much lower than that one has to transmit to the ultrasonic beam when it is applied either on the lateral semicircular canal (Arslan's technique I) or on the bone vestibule (Arslan's technique II). As is known the bone wall of the labyrinth absorbs most of the intensity of the u.s. beam (only 10% of the intensity reaches the membranous labyrinth).

The Kossoff round window u.s. generator of 30 Mc has an output which can be selected from 0 to 70 milliwatts, as states that an output of only 30 milliwatt is sufficient to abolish tinnitus and vertigo in patients with Menière's disease. In order to couple directly the u.s. beam to the tympanic scale facing the round window membrane the plane transducer of Kossoff's generator of 15 mm in diameter can be easily inserted in the round window. The u.s. beam is irradiated only from one flat side of the probe tip; this side, placed in the round window niche is directed towards the vestibule on the assumption that the u.s. beam will be active there.

### METHOD

We applied this new irradiation technique proposed by Kossoff in 18 patients affected with Menière's disease or with other types of labyrinthosis. We applied this irradiation technique to the oval window too.



FIG. 1. Round window irradiation.

FIG. 2. Oval window irradiation.

The endoneural surgical approach to the ear windows is the same as for stapes surgery.

#### A. Round window irradiation

The round window is seen from an oblique angle and in very few cases its membrane can be seen. In some instances it could appear necessary to drill very gently the anterior border of the round window in order to obtain an easier introduction of the tip of the irrigator. The middle ear cavity must be free of blood before applying the irrigator; a drop of physiological solution is put in the round window niche to assure a good transduction of sound in the round window membrane.

After 10-20 seconds a mild irritative nystagmus of 1 degree directed toward the irradiated ear appears. This nystagmus develops on two planes: in the horizontal plane and on the rotatory plane; sometimes vertical nystagmus is also present. In some cases, after 60-90 seconds, the irritative nystagmus attenuates, and a paralytic nystagmus, directed toward the non-irradiated ear of the same entity of the first, appears. Sometimes we noticed that the two nystagmus are contemporaneous.

The patient is discharged as early as 3 or 4 days after the intervention (Fig. 1).

#### B. Oval window irradiation

This irradiation presents two advantages:

1. The oval window faces the vestibule, and not the tympanic scale and the cochlear duct, which are facing the round window.



Fig. 3 Ultrasonic irradiation probe for oval or round window

2 The position of the oval window is not oblique and therefore it is not necessary to limit the irradiation surface to only one side of the transducer.

Incus and stapes are not luxated, neither are they damaged. There is no difficulty with the presence of the stapes at the oval window as the end of the transducer having a diameter of only 1.5 mm can be easily inserted between the crura going on to the inferior part of the stapes and then applied on the platina inferior border and on the ligamentum anulare (Fig. 2).

#### *Ultrasonic Set*

The irradiation of the middle ear windows is performed by applying a new probe from which a maximal output of 0.15 watt can be obtained. The round probe (Fig. 3) of 1.75 mm diameter is attached to a 12 cm long stainless steel holder which transduces ultrasounds.

The holder is completely covered (with the exception of the tip, of 2 mm length) with a thin polyethylenic lamina in order to avoid side irradiation of the u.s. waves. It can be easily introduced in the external ear canal and middle ear. A drop of physiological saline solution is put in the niche of the irradiated window in order to realize a coupling between the tip of the probe and the irradiated membrane or platina.

For round window irradiation it appeared sufficient to have an output varying between 0.025 and 0.060 watt.

For oval window irradiation, where the u.s. must go partly through the bone of the platina we applied a little stronger output (varying, by single cases, between 0.08–0.1 watt).

As far as irradiation times are concerned we observed that in nearly all cases, nystagmus duration was—as an average value—of 3–5 minutes after this time it begins generally to decrease and reverse its direction (Fig. 4).

#### RESULTS

The results are collected in Tables 1 and 2.

No complications have been observed in any cases neither otitis media nor facial involvement.

TABLE 1 *Response to the selective round window irradiation*

U.S. intensity: 0.025-0.090 watt. Irradiation time: 5'

(3 cases)		Tinnitus		Deafness	
Hearing					
Improved	0	Disappeared	5	Disappeared	5
Static	2	Decreased	2	Decreased	3
Impaired	3	Static	1	Static	—
Deafness	2	Increased	—	Increased	—

TABLE 2 *Response to selective oval window irradiation*

U.S. intensity: 0.08-0.1 watt. Irradiation time: 3'-5'

(10 cases)		Tinnitus		Deafness	
Hearing					
Improved	3	Disappeared	5	Disappeared	9
Static	2	Decreased	4	Decreased	—
Impaired	3	Static	1	Static	1
Deafness	2	Increased	—	Increased	—

## DISCUSSION

1. The possibility of reaching with the ultrasonic beam the membranous labyrinth, passing through the round and oval windows, present undoubtedly many theoretical advantages: (a) a greater exactitude in dosing the intensity of the ultrasonics; (b) the leakage of the u.s., which is so high when the irradiation goes through the labyrinth bone (90%) is reduced to negligible values; (c) the great simplification of surgical procedure.

2. The anatomical features of the round window membrane are the following: (a) the round window membrane is placed obliquely and in front of the tympanic scale and also of the cochlear duct; (b) the round window niche is directed toward the cochlea; (c) the distance between the round window membrane and Corti's organ is shorter than to the sacculus (ANSON, 1919) (Figs. 4 and 6).

Then, even if the irradiator is inserted in the round window niche toward the external and its u.s. beam is irradiated from the posterior side of the probe tip, as the posterior bone wall of the niche is longer than the anterior one (Kobrak), the beam reaches inevitably the perilymph of the tympanic scala and is first directed toward the same axis of the cochlea. Therefore, in doing with drill as we did sometimes in our cases, the anterior border of the round window niche cannot change this direction of the u.s. beam.

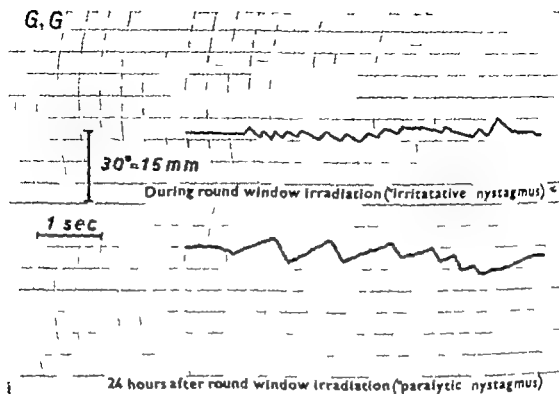


FIG. 4 Case 2 (G, G) Electronystagmographic recording of nystagmus evoked during (above) and after ultra sound irradiation of round window on the left side

3 Furthermore, anatomical features of the round window allow formulation of a hypothesis aiming at interpreting the consequences of the irradiation of the round window.

Disappearance of tinnitus, taking places much more rapidly and permanently than after irradiation by technique I and II and the impairment of the hearing (in some cases reversible) which can take place in some cases only 2 hours after the irradiation, evidence the hypothesis that the convective endolymphatic currents first of all provoked by the n.s. are running in the tympanic scala.

The endolymphatic current reaches the vestibular perilymphatic spaces only after having run through all the cochlear coils and the helicotrema and finally flows into the vestibule.

Of course also small side waves may enter from the round window directly into the vestibule without making the tour of the cochlear coils, but the presence behind the round window of the terminal part of the cochlear duct and of the ductus reuniens and especially the anatomical direction of round window clearly facing the tympanic coil and directed towards the cochlea reduce the number of these diverging side waves. If we consider the very important fact that with the irradiation, by posterior approach of the semicircular canal or of the vestibule we obtain a great nystagmus, and that the perceptible hearing never becomes worse imme-

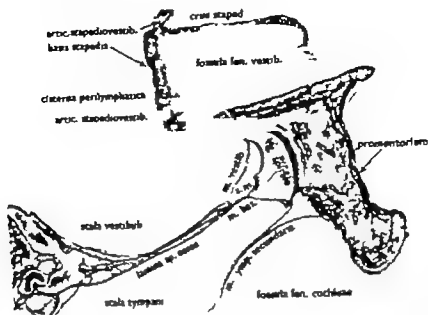


FIG. 5. Fossa fen. cochleae round window Fossa fen. vestibuli - oval window s.z. - cochlear duct (After W. H. Bellucci & Egerton, *Microscopic Anatomy of the Temporal Bone* The Williams and Wilkins Co., Baltimore, 1957)

diately (on the contrary in some cases, it improves even during the first days after the irradiation) and furthermore tinnitus never *totally* disappears by this operation, whereas the irradiation of the round window gives rise to exactly the opposite phenomena (remarkable cochlear changes, but small vestibular phenomena) all these facts support the hypothesis that the greater part of the u.s. waves, arising in the tympanic scala, set out along the cochlear coils.

4. Irradiation of the oval window has two advantages: (a) the anatomical position of the platina is not oblique but exactly facing the vestibule in which semicircular ampullae and otolithical organs are very near; (b) cochlear structures are placed away from the irradiated area (Anson, 1949). Moreover as the thickness of the platina is of a different value in its parts (Anson, 1949) ultrasonics are only partially reflected, and besides they go easily in the vestibule through the ligamentum anulare.

As pathological lesions by Menière's disease are located in the saccule the irradiation of the oval window strikes the crucial point of the hydropleal alterations.

As we observed in our patients, oval window irradiation compared with round window irradiation, at the same u.s. intensity provokes greater vestibular phenomena and less cochlear phenomena even this fact seems to confirm the aforementioned hypothesis (see point 3).

Experiments carried out by Angell James *et al.* (1961) and Arslan

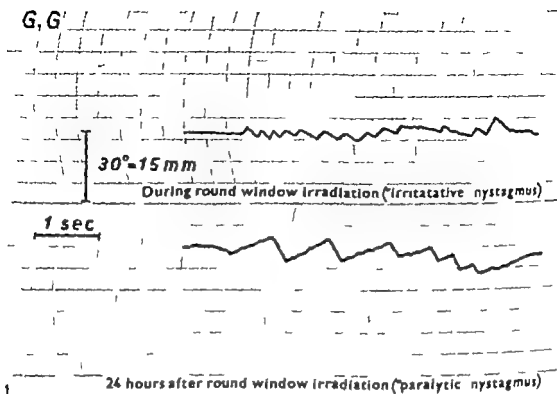


FIG. 4 Case 2 (G G) Electronystagmograph recording of nystagmus evoked during (above) and after ultra-sonic irradiation of round window on the left side

Furthermore anatomical features of the round window allow formulation of a hypothesis aiming at interpreting the consequences of the irradiation of the round window

Disappearance of tinnitus, taking place much more rapidly and permanently than after irradiation by technique I and II and the impairment of the hearing (in some cases reversible) which can take place in some cases only 2 hours after the irradiation evidence the hypothesis that the connective endolymphatic currents first of all provoked by the u.s. are running in the tympanic scala

The endolymphatic current reaches the vestibular perilymphatic spaces only after having run through all the cochlear coils and the helicotrema and finally flows into the vestibule

Of course also small side u.s. waves may enter from the round window directly into the vestibule without making the tour of the cochlear coils, but the presence behind the round window of the terminal part of the cochlear duct, and of the ductus reuniens and especially the anatomical direction of round window clearly facing the tympanic coil and directed towards the cochlea reduce the number of these diverging side waves. If we consider the very important fact that with the irradiation by posterior approach of the semicircular canal or of the vestibule we obtain a great nystagmus, and that the perceptible hearing never becomes worse imme-

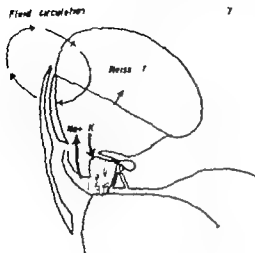


Fig. 7

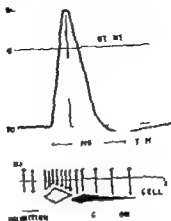


Fig. 8

effect in the neuroepithelial cells, correspond to an hyperpolarisation, that is to say a functional paŷy (with inhibitory effect?) of these cells. This fact is in agreement with the "paralytic nystagmus which appears during oval window irradiation but we can't actually state if this hyperpolarisation is connected only with a direct action of the u.s. waves on the neuroepithelial cells, or even with some cupular flexions (for instance utriculo-sagittal flexion of the lateral cupula) (Figs. 7 and 8).

The "irritative nystagmus appearing during round window irradiation is by all means in contradiction to what happens if the oval window, as we said, the round window is sufficiently far from the vestibular receptors to reduce the influence of the u.s. waves only for creating a convective endolymphatic current which enters the otolithic cavities through the route of the cochlear coil. Furthermore this current direction is not the same as the current coming from the oval window and consequently carries out other functional effects.

At present, lack of experimental knowledge compels us to look for an hypothesis interpreting the phenomena provoked by the irradiation of the round and oval windows, only on the basis of the analysis of the functional and clinical phenomena that we observe in our patients. This analysis, which is extremely rich in data to be evaluated, has been many times recommended by us in order to interpret the effects of the irradiation, by posterior approach, of the semicircular canal (technique I) or of the vestibul (technique II).

In fact analysis of the characters of the different nystagmus arising during and after irradiation, constitutes, for the moment, the true parameter which is valuable for an assessment of the efficiency of the irradiation.





FIG 6 The distances between round window (r) ligamentum spirale and stapes (After G. Beck, *Fests. Vasen Ohrenheilkunde* vols. III I G Thieme 1963.)

*et al* (1964 1966) have shown that the endolymphatic currents provoked by the u.s. are initially thermic currents. They become convective currents and convey the ultrasonic waves, that, at the end, provoke the well-known cellular protoplasmatic lesions in the labyrinth neuro-epithelium. With regard to the phenomena that the ultrasounds certainly raise at the level of the labyrinth membranes and in the biochemical exchange between endolymph and perilymph, etc., we refer to the researches that Angell James *et al* (1961) Hughes & Chou (1964) Dum & Hawley (1962) carried out on the biophysical and biochemical effects that the ultrasounds produce in the organic tissues and membranes of the organism.

It seems very probable, as stated by Hughes & Chou, that the u.s. act on the membranous labyrinth producing marked changes in the ionic balance between the cells and labyrinthine fluids and in the membranes permeability especially extruding  $\text{Na}^+$  and concentrating  $\text{K}^+$  in the neuroepithelium cells and/or in the stria vascularis. Hughes & Chou have experimentally demonstrated the same phenomena in isolated muscle. Such a disruption of the ionic balance could easily explain the cochleovestibular signs observed in our patients during irradiation of the round window (irritative nystagmus, rapid change of tonitus).

Angell James *et al* studying the histological thermal and biochemical effects of the Bristol 3 Mh ultrasonic generator on guinea pigs and sheep, observed in the irradiated labyrinth (1) the perilymph "remained essentially normal in composition" (2) the endolymph showed an increased  $\text{Na}^+$  concentration and a decreased  $\text{K}^+$  concentration.

The  $\text{Na}^+$  and  $\text{K}^+$  variations in the endolymph which have been found by Angell James *et al* (1964) correspond to the aforementioned hypothesis of Hughes & Chou: endolymphatic increase of  $\text{Na}^+$  depends on extruded  $\text{Na}^+$  from the neuroepithelium cells and/or the stria vascularis whereas decrease of  $\text{K}^+$  depends from its cellular increasing. Furthermore it must be assumed that the permeability of the Reissner's membrane may be altered too, after irradiation.

The ionic changes which may occur hypothetically as an ultrasonic

8. A comparison between results obtained after r.w. irradiation and o.w. irradiation allows at present the following clinical indications for irradiation technique

(i) round window irradiation seems to be indicated by cases of severe deafness accompanied by very troublesome tinnitus depending not only on Menière's disease but also on cochlear dropsical lesions sudden deafness of vascular origin

(ii) oval window irradiation seems to be indicated by Menière's disease in which hearing ought to be preserved

Further experimental researches and clinical observations in this field are nevertheless necessary

### ACKNOWLEDGMENT

Our thanks are due to our collaborators G. Molinri, M.D. and G. Babighian, M.D. for helpful clinical observations of patients.

### RÉSUMÉ

L'auteur présente les premiers résultats obtenus après irradiation ultrasonique basse fréquence sur un groupe de malades atteint de maladie de Ménière et autres types de labyrinthose. 1) L'irradiation de la fenêtre ronde paraît être indiquée en cas de surdité grave soit de bordonnement correspondant à une perte sensorielle de l'ouïe ou d'otosclérose avancée et 2) L'irradiation de la fenêtre ovale s'est indiquée que pour la maladie de Ménière dans laquelle l'ouïe doit être préservée.

### ZUSAMMENFASSUNG

Der Verfasser bringt die ersten Ergebnisse nach Ultraschallbestrahlung mit niedriger Freq. über die in einer Gruppe von 20 Morbus Menière und anderen Arten von Labyrinthosen behandelten Patienten erhoben wurden. 1) Die Bestrahlung des runden Fensters scheint in Fällen von schweren Hörschädigungen, die zu gleich sehr beschwerenden Tinnitus zeigen, angezeigt, und zwar nicht nur bei Menière'schen sondern auch bei streu. cursu, traumatisch u. Hörschädigungen von tigen. neurogenen Natur (fortgeschrittener Otosklerose usw.). 2) Bestrahlung des ovalen Fensters scheint nur in den Fällen von Morbus Menière vorzuziehen zu sein, da das Gehör erhalten bleiben soll.

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TABLE 3 *Comparison between responses to selective irradiation of ear windows.*

	Round window	Oval window
<b>Cochlear signs</b>		
(a) During irradiation	Marked variations of tinnitus	No constant variations of tinnitus
(b) After irradiation	1 Improvement of hearing, but sometimes reversible impairment	1 Improvement of hearing
<b>Vestibular signs</b>		
(a) During irradiation	2. Marked improvement of tinnitus 1 Dizziness attack 2 Horiz.-rotat. nystag. directed to the irradiated side 3 At irradiation end in version of ny. direction	2. Improvement of tinnitus 1 Dizziness attack 2 Horiz.-rotat. nystag. with some vertical beats, directed to the non-irradiated side in 80% of cases 3. At irradiation end in version of ny. direction
(b) After irradiation	1 Vertigo for 3-4 hours 2. Transitory nystagmus 3 Marked decrease of vertigo 4 Increase of vestibular reflectivity (caloric test)	1 Vertigo for 1-2 day 2. Transitory nystagmus 3 Disappearance of vertigo 4 No variations of vestibular reflectivity (caloric test)

¶ The possibility of healing dropsical pathology of the labyrinth with a small u.s. energy as our clinical results clearly demonstrate strengthens the statement we formulated in our recent papers concerning u.s. application to surgery: ultrasounds act not only with a destructive effect but with a correction of altered protoplasm belonging to the cellular target. This corrective and selective effect is strictly proportional to the physical parameters of the u.s., that is energy, frequency, output from generator, irradiating surface (intensity), time of irradiation.

However we were not wrong many years ago when we stated the possibility of healing Menière's disease with destruction of vestibular receptors, as has been proved by results of u.s. irradiation with the high intensities given with the techniques I and II of Arslan, but it must be now admitted that the same results can be obtained with a much smaller dose of u.s.

7 The functional and pathological signs which are evoked during and after ear windows irradiation are summarized in Table 3.

has been a recurrence of attack after free interval of several years in some cases. It is doubtful if the small dosage employed can produce any measurable change in cell wall permeability in isolated muscle cells in the light of Mr. Hughes' experiments. There must be a variable loss of transmission through the footplate depending upon thickness and on gelation. If accurate dosage is desired it would be necessary to remove the stapes, apply the U.S. and replace the stapes in the window.

L. B. W. J. Angler: I am sorry that I don't feel very sure about the value of the result of any treatment of Menière's disease as long as we have not both direct and indirect methods to assess the results and double blind statistical analysis of these results. Menière patients do strongly react to all kinds of psychological influences and I am afraid that we are moving in the magical sphere.

M. Arslan (R. Phillips): M. Bordley. The first patients were operated on two ears, got followed over a period of two years, over 50% of them showed an improvement of tinnitus. In some cases, results were spectacular and tinnitus disappeared completely until recently.

I. Mr. H. H. The main effect of irradiation with ultrasound of the labyrinth organ is a selective cellular lesion; the more differentiated and delicate are the cells (such as neuroepithelium) the more destructive are the lesions. When irradiation is performed with low intensity as for the ear windows, another effect is achieved: vasodilatation, cellular and molecular increased metabolism. The oval window irradiation must not create a fistula in the sacculus; on the contrary, the plate must be not damaged at all.

There are hearing canals preserved and we obtained in the ears of our cases.

I. M. Angell James: (1) Ultrasonic frequency was 3 MHz. (2) We did not perform Schlieren photographs. We used Gord's measurement method. (3) Dosages were very low for the output varied from 0.025 to 0.060 watt for a window area from 0.008-0.01 sq. cm. But the appearance of a diagnosis a few seconds after the irradiation began was the only sign of correct dosage as we did not keep low from a too strong diagnosis. Angell James is right, in that he believes that there is a variable loss of transmission through the footplate depending upon thickness. For this reason we based the assessment of the dosage only upon the presence of a diagnosis. (4) The proposal to remove stapes, apply stapes and replace stapes, cannot be made in Menière's patient as stapes detachment would be surely followed by deafness (the hydrostatic sacculus leaves against the stapes).

I. M. Jang: There is doubt that Menière's disease is a deafferentation based upon audiometric and vestibular proof carried out with accuracy is an organic disease. This disease belongs to those which are influenced (as for instance cardiac vascular diseases) by psychic factors and we would be very surprised if a cardiologist would affirm that a discussion concerning cardiac diseases is no longer in the magical sphere. Every logical experimental work with the kind of data result obtained in Menière patient with correct medical or (in few cases) with surgical therapy.

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## DISCUSSION

J E Bordley Mr Arslan's very interesting presentation showing his excellent results was very much enjoyed. I am particularly interested in his unusually good results with tinnitus. Did Mr Arslan follow these patients over a long period of time post-operatively? I raise this question because in some 200 patients where Mr Dandy performed a total section of the 8th nerve when these patients were followed over a long time less than 50% of them had relief of tinnitus.

W House (1) What is the principal of the irradiation (a) Destruction of the vestibular endorgan? (b) Creation of a fistula in the sacculus? (2) What is the end point of the irradiation?

The original concept of ultrasonic irradiation was selective destruction of the vestibular organ and sparing of the cochlear function.

Irradiation of the oval or round window with low dosage ultrasound would not seem capable of endorgan destruction. Therefore the above questions.

J Angell James I congratulate Mr Arslan on his ingenuity and originality. Would he please state what frequency is used. Has he any photographs of the beam? How does he assess the dosage? Is his aim increased permeability or destruction?

Since the caloric responses are not abolished has he followed up his cases for a considerable period?

In our experience even when all caloric responses have been abolished there

has been a recurrence of attacks after free interval of several years in some cases. It is doubtful if the small dosage employed can produce any measurable change in cell wall permeability in isolated muscle cell in the light of Hughes' experiments. There must be a variable loss of transmission through the footplate depending upon thickness and on gelation. If accurate dosage is desired it would be necessary to remove the stapes, apply the U.S. and replace the stapes in the window.

*L. B. W. Jongkees* I am sorry that I don't feel very sure about the value of the results of a treatment of Menière's disease as long as we have not both objective methods to assess the result and double blind statistical analysis of these results. Menière patients do strongly react to all kind of psychological influences and I am afraid that we are moving in the magical sphere.

*M. Arslan (Repl.) to M. Bordley* The first patients were operated on two years ago followed after a period of two years, over 30% of them showed an improvement of the illness. In some cases, results were spectacular as tinnitus disappeared completely until recently.

*J. Mr. House* The main effect of irradiation with ultrasound of the labyrinth organ is selective cellular lesion. The more differentiated and delicate are the cells (such as neuroepithelium) the more destructive are the lesions. When irradiation is performed with low intensity as for the ear window, another effect is achieved: stimulation cellular of the striae increased metabolic activity, etc. The ear window irradiation must not create a fistula in the sacculus; on the contrary, the plate must not be damaged at all.

Therefore hearing can be preserved as we obtained in nearly all our cases.

*J. Mr. Angell James* (1) Ultrasonic frequency was 3 Mhz. (2) We did not perform Schlieren photographs. We used Gordon's measurement method. (3) Dosages were very low for the ear window; the output varied from 0.025 to 0.060 watt for a window area was from 0.008-0.1 watt. But the appearance of nystagmus after a few seconds after the irradiation began was the only sign of a correct dosage as we always kept clear from too strong nystagmus. Angell James is right in that he believes that there is a variable loss of transmission through the footplate depending upon thickness. For this reason, we based the assessment of the dosage only upon the presence of nystagmus. (4) The proposal to remove stapes, apply ultrasound and replace stapes, cannot be made in Menière's patient. Stapes detachment would be surely followed by deafness (the hydropic sacculus against the stapes).

*to Mr. Jongkees* There is no doubt that Menière's disease if its identification is based upon audiometric and caloric proofs carried out with accuracy is an organic disease. This disease belongs to those which are influenced (as, for instance cardiovascular diseases) by psychic factors and we would be very surprised if a cardiologist would affirm that discussion concerning cardiac diseases is "moving in a magical sphere." Every otologist experimented with the good and definite result obtained in Menière patient with correct medical or (in few cases) with surgical therapy.

## NEW TECHNIQUES OF PLASTIC SURGERY TO REPAIR THE PHARYNGO-ESOPHAGEAL SEGMENTS USING CERVICO ACROMIAL FLAPS

### *A Previous Report*

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The author describes several methods of utilizing the cervico-acromial flap (shoulder flap) be it to close pharyngeal fistulas in patients with heavy irradiated skin or to close large pharyngostomae fashioned after some pharyngo-laryngectomies. These techniques have been used also in cases of cicatricial atresia of the pharynx and esophagus and in cases of esofagocolophasties when the cephalic segment of the colon has been lost by necrosis. Advantages: (1) utilization of a flap from a not distant region with such a good blood supply that assures the vitality of the flap even when it has to be angulated or twisted to attain the area to which it should be applied. (2) Possibility of using the bloody surface of the flap or the surface covered by the skin to fashion a tube for the reconstruction of the pharyngo-esophageal segment.

During the Vth Brazilian Congress of Oto-Rhino-Laryngology held in São Paulo in Sept. 1966 the author presented, in collaboration with Almeida, a previous report on: Plastic reconstruction of the pharyngo-esophageal segment with cervico-acromial flaps and will now present to members of the Collegium other techniques for repairing the pharyngo-esophageal segment, using the same kind of flaps.

Cervico acromial pedicle flaps used for the first time by Mitter in 1842 in the treatment of a large retracting scar burn of the skin of the neck, have not been used, to the best of our knowledge by anybody else before us for the reconstructive surgery of the pharyngo-esophageal segment with the techniques we have been trying to standardize since 1960.

These techniques, we hoped would be helpful for head and neck surgeons who are frequently confronted with cases of large pharyngostomae or fistulae of the pharynx, in patients with heavy irradiated skin which can only be closed by means of skin flaps brought from a distance.

Another group of cases difficult to solve is that made up of serious retracting scars or cicatricial atresia of the pharyngo-esophageal segment due to the swallowing of caustic substances.

Spina (1954) has emphasized the advantages of pedicle flaps for the repair of large retracting scars of the skin of the neck. He has mentioned that these flaps, on account of their rich blood supply can be applied to

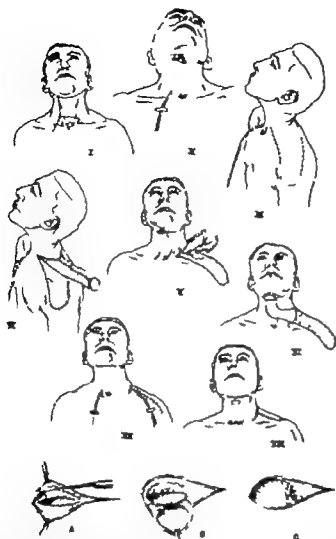


FIG. 1 Diagrams and detail of the thoracic techniques for the repair of the pharyngo-esophageal segment, using cervico-acromial pedicle flap. Case I which pharyngo-laryngectomy with right neck dissection was done 20 days before Reconstructive surgery has been done in three stages 1st stage Diag. III; 2nd stage Diag. IV and V and III A B and C, and Diag. VII 3rd stage Diag. VIII Description page 240

areas with poor nutrition, and that they could help to transform the neighboring fibrous tissue into younger connective tissue.

In discussing the pathophysiological bases of the surgical treatment of scars from burns, Spina examined the factors held to be responsible for the retraction of the scars, the secondary retraction of the grafts and the reason for the difference in behavior between graft and flaps. What he stated in relation to skin we have found to be also true in relation to the digestive tract affected by the swallowing of caustic substances.



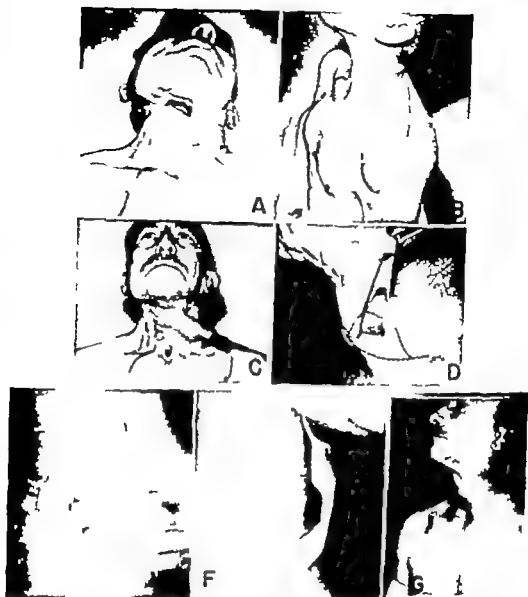


FIG. 2. Pictures taken during different stages to show the large pharyngeal tumor. The cervicoacromial flap is raised and sutured at its original place in the first stage (A). The tubular flap has been passed behind the larynx and sutured at a point of the neck and sutured to the base of the tongue and posterior wall of the pharynx (B). The interrupted line shows where the pedicle flap ought to be cut to be sutured to the esophagus (C). (D) X-ray picture and clinical view of the patient to show functional and cosmetic result (E, F, C).

First and second degree burns of the skin generally heal without leaving sequelae and their seriousness is related to the depth and extension of the burn and to the delay in epithelization. Other factors stimulating the formation of fibrous tissue are the successive traumas on the granulation tissue of the wound.

The same factors were previously pointed out by Bellinof & Charancoff (1935) regarding the action of caustic substances on the food passages. They constitute the pathophysiological bases for the treatment of the acute

and chronic corrosive esophagitis which have been established by Bellinof with his sequential papers published from 1930 up to 1942.

And these are the reasons why we are trying to take advantage of the pedicle flaps in the treatment of cicatricial atresia of the pharynx in cases of live horns.

With regard to the treatment of pharyngeal fistulae which appear post operatively in laryngectomized patients previously submitted to intensive radiation therapy we have since 1960 with the collaboration of plastic surgeons been using cervico acromial flaps with great satisfaction.

Two cervical-acromial flaps may be prepared simultaneously or migration of the flap as far as the area to be covered may be obtained with one or two delays, without great discomfort to the patient.

The rich blood supply of these flaps allow us not only to greatly surpass the ratio 1 : 1.5 between the width of the pedicle and the length of the flap, but also assures the vitality of the flap even when it has to be angulated or twisted to attain the area to which it should be applied.

The new techniques we are working on allow us to use the cervico-acromial flaps to fashion a tube for the reconstruction of the pharyngo-esophageal segment. They have proven particularly advantageous because the raw surface of the pedicle is placed under the skin of the antero-lateral aspect of the neck, which gives very good cosmetic results.

This detail also prevents infection of the flap, which on account of a rich blood supply may act upon neighboring adult scar tissue helping it to change into younger connective tissue.

Another advantage is that the donor area can be easily closed by a simple approach to the edges of the skin or by free skin grafts, this being hardly noticeable afterwards.

The only inconvenience of our technique seems to be the delays necessary in the mobilization of the flap, which we have been carrying out according to the recommendations of the plastic surgeons.

The diagrams shown in Figs. 1 and 2 should give a better understanding of the techniques we are using to repair the pharyngo-esophageal segment.

In Fig. 1 we have tried to show the different stages of the surgical treatment given to a patient with a cancer of the right pyriform sinus with a large extension to the posterior wall of the pharynx.

We were obliged to perform a pharyngo-laryngectomy with a right radical neck dissection, but, knowing that we would have to resect an entire segment of the pharynx, we started the operation by raising the skin flaps so as to allow the plastic repair to be done later (Diag. I in Fig. 1).

Through Diag. II and the picture reproduced in Fig. 1 A we may estimate the condition of the patient when we started the reconstruction of the food passage.

The plastic repair has been performed in three stages.

*First stage* The cervico-acromial flaps were raised and immediately sutured at their original place (Diag. III).

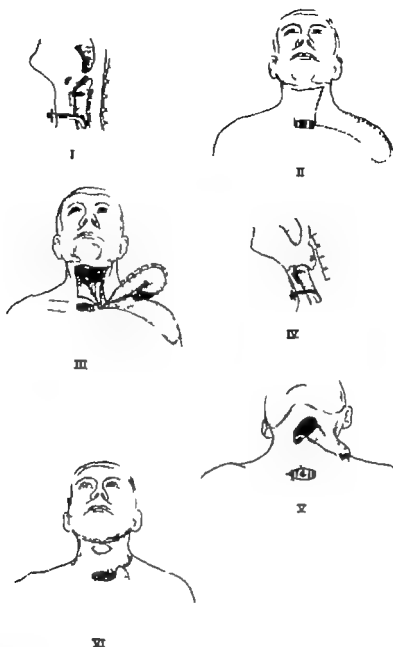


FIG. 3 Diagrams of the author's technique used in the repair of the trachea and food passages in the case of cicatricial atresia of the pharynx and cervical esophagus due to the swallowing of ly.

*Diagram I* Condition of the patient before the operation. *Diagram II* The skin flap raised and sutured to the tracheal place (1st stage). *Diagram III* II and V Different stages of the 2nd stage in which pharyngeal muscles were sutured all around the trachea and the tubular flap sutured to the pharynx and larynx. *Diagram VI* III illustrates the 3rd stage in which the pharynx was closed and the tubular flap sutured to the segment of the esophagus brought up behind the trachea.

**Second stage** (a) The pedicle flap was raised after a delay of 15 days, to fashion a skin tube.

(b) The edges of the pharyngostoma were freed (detail 4).

(c) A tunnel was made under the skin of the antero-lateral aspect of the

neck, and the tubular pedicle flap turned to pass through it and be sutured at the base of the tongue and postero lateral walls of the pharynx (Diag IV V and VI, and details B and C)

(d) The skin of the anterior and lateral aspect of the neck was closed. A continued aspiration was applied into the tubular flap and a feeding tube passed through the esophagostoma (Diag VII)

Third stage After another delay of two weeks the lower segment of the flap was cut and moved to be sutured with the proximal extremity of the esophagus (Diag VIII and close-up picture in Fig. 2)

In the picture reproduced in Fig. 1 A one can also notice that we have fashioned the esophagostoma at the right side, trying not to interfere with the fashioning of the tubular flap

This last detail caused us, in our first case a little more difficulty at the third stage—a slight bending of the new pharyngo esophageal segment, which lately we saw could be avoided. However in spite of this, the cosmetic and functional results were very satisfactory as can be judged from other pictures also reproduced in Fig. 2

Fig. 3 shows some diagrams to illustrate how we have used a cervico acromial tubular pedicle flap to treat a case of cleidocranial atresia of the hypopharynx and cervical esophagus.

Even though we had already successfully used Ogura's technique in other cases, in this particular case we decided to use a tubular pedicle flap, in order to avoid secondary retractions which are always greater with free skin grafts.

The diagram reproduced in Fig. 3 will serve to illustrate the procedure performed in three stages, necessary to reestablish the air and food passage

First Stage Skin flaps have been raised and immediately sutured in their original place (Diag II)

Second Stage After a delay of 1 day a pharyngectomy has been performed and all the scar tissue involving the hyoid bone the epiglottis, pharyngo-epiglottic folds and a segment of the posterior wall of the pharynx has been removed. A tubular skin flap was fashioned and its distal end sutured to the larynx and pharynx (Diag III IV and V)

Third Stage A segment of the colon was brought to be sutured to the skin tubular flap and the pharynx has been closed.

#### RÉSUMÉ

L'auteur présente diverses méthodes d'utilisation d'un lambeau cervico-acromial (lambeau d'épaule) soit pour la fermeture pharyngo-œsophagienne, soit pour la reconstitution totale d'un segment pharyngo-œsophagien. Ces techniques ont été employées en cas de pharyngo-laryngectomies avec fistules ou large pharyngostomie d'isthme du segment céphalique du colon surfaite ainsi que employé pour l'œsophagocoloplastie (en cas d'isthme fœtal de l'œsophage et d'hypopharynx). Avantages: 1. Utilisation d'un lambeau facilement mobilisable recouvert de la peau glabre très résistante. 2. Possibilité d'utiliser soit la surface du lambeau, soit la surface couverte par la peau.

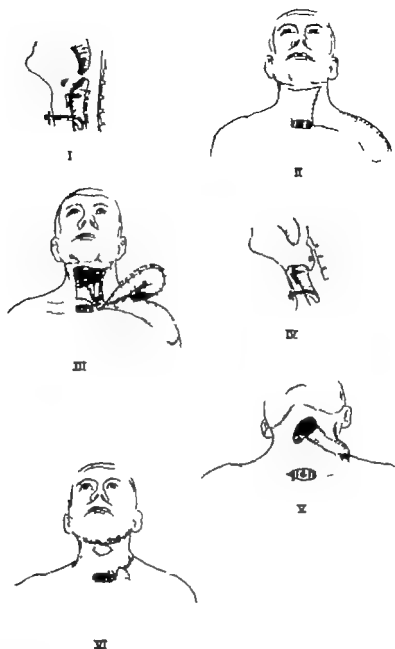


FIG. 3. Diagram of the author's technique used in the repair of atresia of the pharynx and cervical esophagus due to the small wing of the pharynx.

*Diagram I* Condition of the patient before the operation. *Diagram II* The skin flaps raised and sutured at their original place (1st step). *Diagram III* The different stages of the 2nd stage of the operation with a pharyngotomy was done and the tubular flap sutured to the pharynx and larynx. *Diagram VI* Illustrates the 3rd stage in which the pharynx was closed and the tubular flap sutured to the segment of the colon, brought up behind the trachea.

**Second stage** (a) The pedicle flap was raised after a delay of 15 days, to fashion a skin tube.

(b) The edges of the pharyngostoma were freed (detail A).

(c) A tunnel was made under the skin of the antero-lateral aspect of the

material for such purposes and that right colon (ascending) was proposed to fast, its mesenteric artery and vein to be sutured to the corresponding neck vessel (carotid external art., jugular vein) (Fairman Bristol & McNeill, Portsmouth) I London Prof Harrison and Ph Reading have applied this method in a number of cases with good results. Recently J F Simpson of St. Mary's Hospital, London has used in 3 cases the sigmoid colon transplantation in collaboration with Mr Eastcot, specialist in angiosurgery all cases healing successfully.

P M Barrett (Reply) to M Hollinger Thanking Mr Hollinger's comments I should say that we only used irradiation after the malignant degeneration of the papilloma.

to M Leskiewicz I also have to thank Mr Leskiewicz for his kind remarks and should add that we have developed our present techniques after trying most of the other methods he has mentioned. We are really convinced that our techniques may bring some contribution to this problem.

## ZUSAMMENFASSUNG

Der Verfasser beschreibt verschiedene Methoden zur Benutzung des zervikokromialen Lappens (Schulterlappens) sei es zum Verschluss von Pharyngostomien sei es zur kompletten Wiederherstellung des pharyngo-ösophagealen Abschnittes. Diese Methoden wurden benutzt bei Patienten die Pharyngolaryngostomien unterworfen wurden und in Fällen von Nekrose des zephalen Abschnittes des Kolonbogens der zur Ösophagokoloplastie benutzt wurde in Fällen von Narbenatresien des Ösophagus und der Hypopharynx Vorteile 1 Benutzung eines leicht mobilisierbaren Lappens mit glatter Haut die auch sehr widerstandsfähig ist 2 Möglichkeit die blutige Fläche des Lappens zu benutzen oder die mit Haut bedeckte Fläche

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## DISCUSSION

P. H. Holinger: We thank Mr Barretto for this interesting demonstration of the effective solution of a difficult problem. May I ask Mr Barretto a question only indirectly related to his paper? Did the child who developed cancer in a papilloma of the larynx receive irradiation to the larynx and if so what was the interval of time between the irradiation and development of the cancer?

A. Lasker: Repair of the gape after laryngopharyngectomy has been one of the important problems ever since the first such operation was performed in 1883 by Bernhard v. Langenbeck. The simplest method using two square angular flaps from both sides of the gape was devised by Cluck, Sorensen, Hocheneegg, Varnachik, v. Eicken, Henkels, Seblleau, Ormerod, Ogura, Ellis, M. Lewis & Pietrantoni. A rubber pharyngeal prosthesis of different sizes, surrounded by a Thiersch graft adapted to the upper end of oesophagus, was used by Sir Victor Negus in 1952. In 1953 Asherson, J. F. Simpson & Some used the anterior part of the larynx, with epiglottis as a covering flap to repair the gape after excision of the posterior part of the larynx in non-advanced cases of postcricoid carcinoma. Then colon transplantation gained priority as the reasonable autoplasmic

Guedry on the other hand, "assumes that the canals are at best insensit to the linear accelerometers" He is of the opinion that although otoliths do not generate nystagmus impulses *per se* they can either modulate or maintain canal responses, under the influence of different acceleration conditions. Further it has been well known for decades that various kinesthetic organs can alter canal responses. For a long time no data were known suggesting the otoliths as a possible etiologic factor for generating nystagmic impulses until Jongkees & Phillipson (1962) demonstrated nystagmic responses in rabbits in a lateral position and in humans looking to the extreme left or right. These responses were seen during the application of purely linear accelerations on a parallel swing—suggesting otolith nystagmus probably on the basis of compensatory eye-movements and central corrections.

In our laboratory we also are confronted with a most intriguing problem of labyrinthology i.e. which sub-organ is responsible for which eye-movements. We conducted some experiments on rabbits in which a combination of two stimuli was applied to a pair of normal labyrinths—a constant rotation about a horizontal axis together with a slow sinusoidal movement (0.1 Hz) about a vertical axis. It seems a very simple matter but the mathematical evaluation of the generated spacial vector is as follows

$$\vec{a}_g(t) = \vec{\omega} \times [\vec{\omega} \times \vec{r}(t)] + 2\vec{\omega} \times \dot{\vec{r}}(t) + [\vec{\omega}_1 \times \vec{r}(t)] + \frac{d\vec{\omega}_2(t)}{dt} \times \vec{r}(t) + \vec{\omega}_2(t) \times [\vec{\omega}_2(t) \times \vec{r}(t)]$$

$\vec{a}_g$  resultant vector

$\vec{\omega}_1$  angular velocity of barbecue rotation,

$\vec{\omega}_2$  angular velocity of rotation about vertical axis,

vector product,

$r$  distance between intersection axes and point of rotation (labyrinth),

$t$  time

From the mathematical formula the experts can read that the generated vector is the product of the centrifugal forces evoked by the horizontal and the vertical axial rotation, the external product of the variation in velocity as a function of time of the vertical axial rotation, plus the coriolis term. The motif of choosing this seemingly extremely complicated stimulus was that it offers an easy method of measuring threshold values because the vector alters from zero to maximum and to zero again. A second check is possible since the rotation about the vertical axis changes from clockwise to counter-clockwise sinusoidally.

Lastly the stimulus is three-dimensional, resulting in a stimulation of all the cupulae. The resultant eye-responses were recorded with a type Elema A.C. amplifier with a time constant of about 10. Horizontal and vertical lead wires were used for recording. The experiments were performed in the dark. After the electrodes were securely placed intradermally the animals were fastened in such a position that the lateral semi-circular canals were in a horizontal plane. After this, the barbecue rotation and then the vertical axial rotations were recorded separately, the combined



# BARBECUE ROTATION IN COMBINATION WITH SINUSOIDAL ROTATION ABOUT A VERTICAL AXIS

## *A Preliminary Note*

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Amsterdam, The Netherlands*

The eye-movements caused by a combination of rotations about a cephalo-caudal horizontal axis and sinusoidally changing accelerations about a vertical axis were recorded. A mathematical analysis of the spatial vector is given. The response is recorded by means of electro-nystagmography and analyzed into an otolithic and a semicircular component. It appears that not only the left and the right labyrinth, but also in one single labyrinth the otoliths and the semicircular canals are stimulated differently by the same vector.

During the last few years rotation about a horizontal cephalo-caudal axis has caused much interest because the results obtained differed from the classic responses to rotation. In the last case the axis of rotation was vertical. The well known results and conclusions do not hold if the axis of rotation is horizontal. Various authors, e.g. Guedry (1965), Correia & Guedry (1964) and Benson & Bodin (1966) conducted interesting experiments concerning the so-called barbecue rotation and tried to solve some of the problems which arose during it.

What are these results? The salient features are: to begin with, a nystagmus during constant rotation about a horizontal axis. According to the classic conception there is no reason for this nystagmus to appear because of the absence of lymphokinesis. Secondly, the nystagmograph records an eye-deviation which alternates synchronously to the reorientation of the labyrinths to gravity. At present we are not sure whether this is an otolith or a canal generated impulse. These factors add to the problem of which suborgan is responsible for the various eye-movements.

Benson forwarded an attractive theory, his so-called "Slush" theory, in which he explains that the configuration of the membranous canals would change according to its orientation to the linear acceleration or if the direction of gravity is changed in relation to the canals from a perpendicular direction to a co-planar direction that this could cause a change of the cupula-damping factor. This modification of the endolymph hydrodynamics could explain some of the above mentioned phenomena.

Guedry on the other hand, "assumes that the canals are at best insensitive linear accelerometers" He is of the opinion that although otoliths do not generate nystagmus impulses *per se* they can either modulate or maintain canal responses, under the influence of different acceleration conditions. Further it has been well known for decades that various kinesthetic organs can alter canal responses. For a long time no data were known suggesting the otoliths as a possible etiologic factor for generating nystagmic impulses until Jongkees & Philipsson (1962) demonstrated nystagmic responses in rabbits in a lateral position and in humans looking to the extreme left or right. These responses were seen during the application of purely linear accelerations on a parallel swing—suggesting otolith nystagmus probably on the basis of compensatory eye-movements and central corrections.

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$\vec{\omega}_1$  vertical vector

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From the mathematical formula the experts can read that the generated vector is the product of the centrifugal forces evoked by the horizontal and the vertical axial rotation, the external product of the variation in velocity as a function of time of the vertical axial rotation, plus the coriolis term. The motive for choosing this seemingly extremely complicated stimulus was that it offers an easy method of measuring threshold values because the vector alters from zero to maximum and to zero again. A second check is possible since the rotation about the vertical axis changes from clockwise to counter-clockwise sinusoidally.

Let the stimulus be three-dimensional, resulting in a stimulation of all the cupulae. The resultant eye-responses were recorded with a type EM 50 A.C. amplifier with a time constant of about 10. Horizontal and vertical lead were used for recording. The experiments were performed in the dark. After the electrodes were securely placed intradermally the animals were fastened in such a position that the lateral semi-circular canals were in a horizontal plane. After this, the barbecue rotation and then the vertical axial rotations were recorded separately the combined

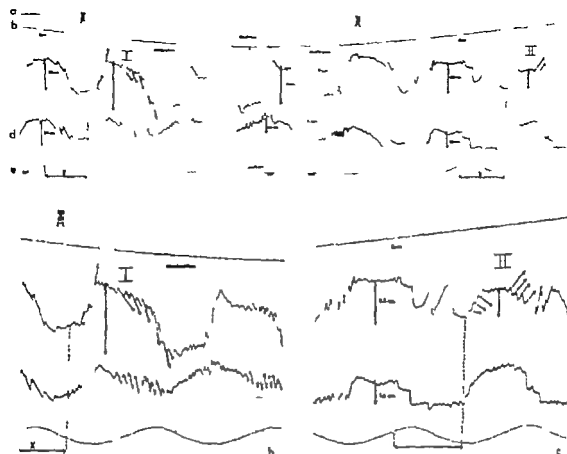
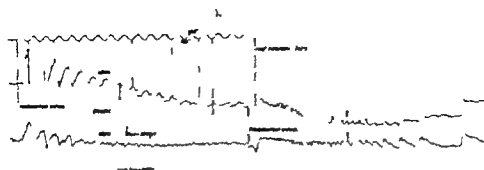


FIG. 1. Eye-movements of a rabbit during combined rotation about a horizontal and vertical axis. (a) Time in seconds. (b) Sinusoidal rotation (.01 Hz) about a vertical axis. (c) Movement of light eye. (d) Movements of left eye. (e) Barbicorne rotation (Le about horizontal axis) with constant speed. (a) Clockwise movement of (b) (b) and (c) Two responses taken from Fig. 1 c used by identical barbicorne stimulus but opposite vertical axis acceleration. In left vertical axis acceleration clockwise I II counter-clockwise. The oblique arrows indicate the direction of the low phase of the nystagmus. The vertical arrows the amplitude of the periodic eye-movement.

stimulus of the barbicorne and vertical axial rotation following. For the sake of clarity the recorded results are discussed with the aid of a few typical nystagmograms.

Here follow a few graphs to demonstrate our findings.

In Fig. 1 the acceleration about the vertical axis changes from clockwise to counter-clockwise. This implies an inversion of the endolymphatic flow and an opposite deflection of the cupulae. As one would expect, the nystagmus direction also inverts. What is interesting though is not that the nystagmus-direction inverts, but that the rhythm and phase of the eye-deviations stay constant and thus do not invert *pari passu* with the inversion of the endolymphatic flow and the resultant nystagmus. This can only be explained if one assumes that both eye-movements are generated by different sub-organs of the labyrinth namely the canals and the otoliths respectively. The reason for the inversion of the nystagmus direction is



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FIG. 2. Stopping the movement about the vertical axis at the moment of maximum speed does not produce deviation of the average eye position.

wholly in accordance with our classic conception of labyrinth physiology namely the inversion of the endolymphatic flow. The explanation that the rhythmic pattern of the eye-deviations is not altered is that the otoliths are stimulated by the alteration and re-orientation to the direction of the gravity vector and is thus in phase to the barbecue rotation as indicated by the eye-deviation. The alteration of movements about the vertical axis does not influence the linear vector at all. The proof that the centrifugal force evoked by the vertical axial rotation has no practical influence on the direction of the gravity vector is demonstrated in Fig. 2. When the vertical axial rotation is halted at the point of maximal linear stimulation (within 3 seconds, thus a period well below the 10 msec time constant of our AC amplifier and the iso-electric line can be regarded as accurate) no deviation from the iso-electric line takes place. During one cycle of the barbecue rotation at maximum angular speed of the vertical axial rotation the direction of the nystagmus inverts two times during one cycle on account of the changing coriolis accelerations. If the vertical axial rotation alters from clockwise to counter-clockwise the direction of the nystagmus is inverted. One further notices that the phase of the eye-deviation does not invert. It explains two facts.

1. The direction of the nystagmus is inverted because of the coriolis force in rotation which is brought about by the change of the movement about the vertical axis from clockwise to counter-clockwise or vice versa.

2. The eye-deviation is not inverted since the coriolis force generated by the above-mentioned movement is too little to alter the direction of the gravity vector.

This demonstrates that, although in this case the cupula system responds to the coriolis stimulation, the eye position does not.

The conclusion that can be drawn from the above discussion is that the different movements are caused by two different sub-organs—the canals and otoliths.

Another point of interest is the amplitude of the eye-deviation per cycle.

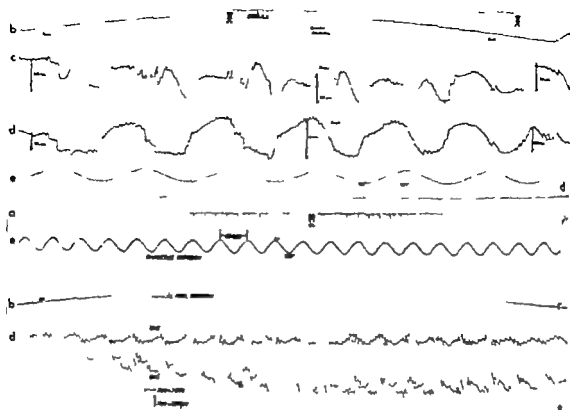


FIG. 3 The eye-movements provoked by the same stimuli as in Fig. 1 but for the direction of the rotation about the vertical axis which is the counter-clockwise part of the turn. (d) Speed 1 rotation/10 seconds. (e) Speed 1 rotation/2.5 seconds. See Fig. 1

Regarding two comparable responses of the same eye at the same barbecue stimulus, but with the difference that the vertical axial acceleration has changed from *cw* to *c.c.w.* one notices that the amplitude of I is greater than that of II. This is explained as follows. In the case of I the direction of the slow phase of the nystagmus is co-directional with the eye-deviation and in the case of II the slow phase of the nystagmus is in the opposite direction to the eye-deviation. It seems that the slow phase of the nystagmus increases the amplitude of the compensatory eye-deviation in one (case I) and reduces it in the other (case II).

This observation suggests two facts

(a) A further proof that two different components are generated by two different sub-organs. It would seem improbable for the cupulae to be thrust in one direction by the endolymphatic flow and yet at the same time be it by some other mechanism (Slosh) to generate an impulse in the opposite direction which would be responsible for the eye-deviation movement. Concerning the canal influence on the eye-deviation it appears that the pure amplitude of the eye-deviation would be the average amplitude of the amplitudes of I and II which is 3 cm in the recording of the above case. This corresponds to the value which we recorded for a barbecue rota

tion without concomitant rotation about a vertical axis at the same angular speed.

In Fig. 3 the effect of a faster angular speed of the barbecue rotation is recorded. It appears that the amplitude of the eye-deviation is suppressed while the intensity of the slow phase of the nystagmus is increased, so much that it is hardly possible to distinguish the slow from the fast phase. This also demonstrates the difference of the behaviour characteristics between the two different eye-movements. The nystagmic response is intensely stimulated by the increased magnitude of the impulse but the eye deviation has become less intense. Although this last phenomenon is not easily explained it suggests again that the two different eye movements are generated by two different sub-organs, both with their own characteristics.

### CONCLUSIONS

From the above recordings and observations it seems that at least two different sub-organs must be responsible for the two different eye responses. It further appears that there exists a close coordination between these sub-organs. The amount of reciprocal influence depends on the combination of different accelerations, both rotatory and linear.

### RÉSUMÉ

Les mouvements des yeux, provoqués par une rotation constante autour d'un axe horizontal, céphalo-caudal combinée avec une accélération sinusoidale autour d'un axe vertical ont été enregistrés par électro-nystagmographie. Une analyse mathématique du vecteur spatial est présentée. Les courbes ont été analysées. Elles montrent des éléments lithiques et canaliculaires. Une seule excitation ou stimulation différentielle sur le labyrinthe droit et gauche mais aussi sur la partie otolithique et canaliculaire d'un seul labyrinthe.

### ZUSAMMENFASSUNG

Die Augenbewegungen, welche während einer konstanten Drehung um eine horizontale, cephalo-caudale Achse zusammen mit einer sinusförmig wechselnden Beschleunigung um eine vertikale Achse entstehen werden elektro-nystagmographisch registriert. Die mathematische Analyse des räumlichen Vektors wird gegeben. Die Kurven werden analysiert und zeigen Otolithen und Bogengangselemente. Es zeigt sich, daß beide Labyrinthe sowie auch Otolithen und Bogengänge des einzelnen Labyrinthes vom selben Vektor ungleich gereizt werden.

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## DISCUSSION

*C Ferndnde* We have also observed in our animals rotating about two axes the same modulation of the base line as shown by Mr Jongkees. All the recordings were done with DC coupling

## ABSORPTION AND TRANSFERRING OF THE COCHLEAR FLUIDS

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The perilymph is absorbed in the loose connective tissue of the modiolum, the endolymph is absorbed in the *planum limbi* and the interstitial liquid of the organ of Corti in the inner spiral sulcus. The basila of the wall of the aqueduct of the cochlea in a fetal phase transfers almost only perilymph. When fully developed many veins of the above-said basila are obliterated and the remaining ones transfer more blood than perilymph. From the interstitial spaces of the limbus the endolymph flows into the capillaries towards the inner auditory vein and the interstitial liquid of the organ of Corti flows towards the same veins by means of short lymphatic vessels.

It is known, according to Siebenmann, that the loose connective tissue absorbs endolymph which is transferred towards the perinervous and sub-arachnoid spaces, while they holds it to be transferred by means of the venous net. The cochlear endolymph is suggested to be absorbed by the endolymphatic sac (Guild, 1927) or by the outer spiral sulcus (Saxén, 1941) or by the limbus (Borghesean 1950, 1952, 1957) unknown is the existence of lymphatic vessels in the cochlea.

The persistent lack of ideas about these arguments has induced me to study from an histological point of view two human cochleas, one of a 6 m fetus and another of a fetus at term. I have chosen cochleas in a phase of advanced development because, during this period, the cochlear fluids contain a great quantity of albumen and of cellular detritus which leave traces of the paths followed for the absorption.

In the 6 m fetus is clearly discernible the great amount of albumen in the cochlear fluids and, in the modiolum the large size of many vessels full of a gray substance with very few red globuli (Fig. 1). These vessels have only endothelial tunics with scattered connective cells. They originate from small vessels of the loose connective tissue of the modiolum (Fig. 2) and run towards the vein of the aqueduct of the cochlea. This connective tissue is infiltrated by a gray substance and the cells of the very thin histiocyte net contain many black granuli. The endothelial membrane lining the tissue is constituted of cell with clear and swollen protoplasm (Fig. 3).

The cochlear fluid of the fetus at term are clear. The loose connective tissue of the modiolum is infiltrated by a gray substance faced by a barrier of macrophages (Fig. 4) some of which are in the shape of clasmatoocytes (Fig. 5). The lining endothelium of the loose connective tissue assumes a



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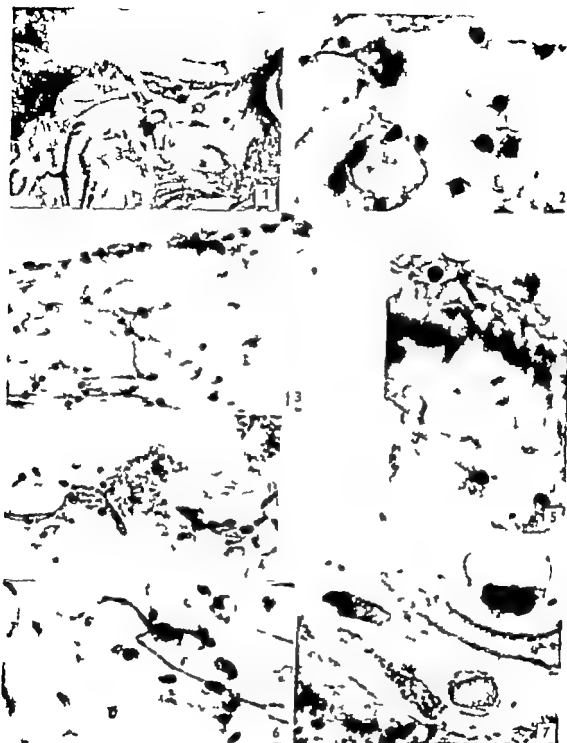
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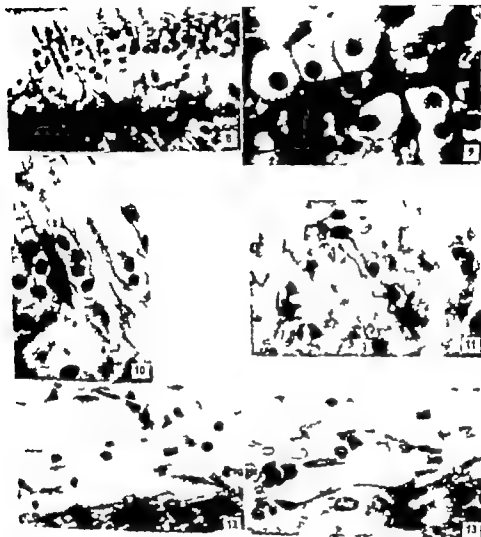
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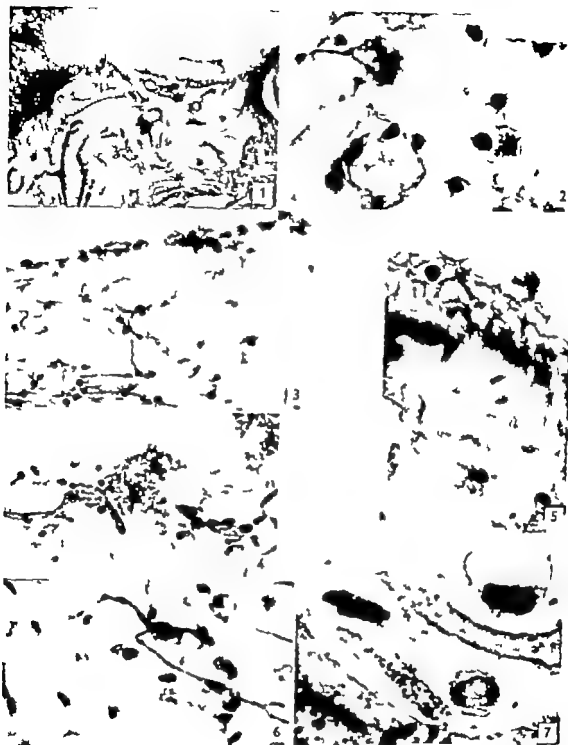


reticular aspect on account of the transparency of the cells constituting it and of the gray substance infiltrating the intercellular spaces (Fig 6). The vessels of the modiolum which in the 6 m fetus contained gray substance here are empty or show few red globuli recent coaguli, small parietal or obstructing thrombi in various phases of change while the connective tissue surrounding these vessels is in the first phase of sclerosis (Fig 7).

The limbus of the 6 m fetus is seen in an oblique section showing the



inner spiral sulcus, the interdental sulcus containing the epithelial cells and the connective tissue (Fig. 8). Many interdental sulci cross one another in various ways and are amply open in the endolymphatic subtectorial spaces and in the inner spiral sulcus, while they are connected to the interdental spaces of the connective tissue by means of anfractuous gapings (Fig. 9). The cells of the interdental sulcus have globose nuclei, abundant protoplasm and constitute an epithelial formation that covers and penetrates into the anterior face of the limbus the *planum limbi* (Fig. 10) which is almost the same as the *planum emarginatum*. The connective tissue of the limbus assumes an areolar aspect, since it is constituted of many interstitial spaces of different width and shape (Fig. 11); some of them originate near the inner spiral sulcus and extend radially along the spiral lamina, quite close to the nervous fibres. These spaces begin as



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die Perilymphe resorbiert werden. Die Struktur die Morphologie des Epithels und des Bindegewebes des Limbus zeigen dass die cochleäre Endolymphe absorbiert wird

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lymphatic gaps more or less wide and with uncertain margins further on they are provided with a very thin endothelial tunic (Fig 12) conferring a vascular aspect but they contain no red globuli and join the veins of the modiolum (Fig 13)

The histological findings show that in the 6 m fetus the whole basin of the vein of the cochlear aqueduct acts as a great lymphatic way because it conveys a massive quantity of perilymph absorbed in the loose connective tissue of the modiolum. It deals with a remarkable and transient phenomenon connected to the development of the cochlea, since in the fetus at term the veins full of perilymph are no longer traceable but the evidence that the above mentioned phenomenon has taken place also in this last fetus is offered by the reticular histiocytic reaction and by the vascular alterations causing obliteration. These changes reduce the flow of the basin of the vein of the cochlear aqueduct and can signify that the perilymphatic balance in the phase of cochlear development is more active than later on.

The remarkable structural likeness between interdental epithelium (*planum limbi*) and *planum semilunatum* suggests a similar function. Voldrich thinks that the limbus secretes endolymph while in my opinion, many facts (morphology and structure of the limbus, existence in the cochlear duct of sufficient formations secreting endolymph, etc.) force one to consider that the limbus is apt to absorb the endolymphatic fluids (endolymph and interstitial liquid of the organ of Corti) separately.

From the interstitial spaces of the limbus the cochlear endolymph is transferred by hematic capillaries towards the inner auditory veins, while very likely the interstitial liquid of the organ of Corti at least in this phase of development seems to be transferred from the inner spiral sulcus towards the same venous system by means of lymphatic vessels.

I think I have new elements to confirm what I wrote in 1930 about the absorption of the cochlear fluids.

## RESUME

Par les recherches d'aujourd'hui on peut tirer que les liquides cochléaires sont absorbés séparément : le périlymphe par le tissu conjonctif de la columelle l'endolymph par le *planum limbi* et le liquide interstitiel de l'organe de Corti par le sillon spiral interne. Le bassin veineux de l'aqueduc du limacon dans une phase fœtale contient seulement de la périlymphe après le développement de la cochlée beaucoup de ces veines s'oblitérent et les restantes transfèrent plus de sang que de périlymphe. L'endolymph est transférée par les capillaires qui arrivent au lacs des veines auditives internes et le liquide interstitiel de l'organe de Corti est transféré par de brefs vaisseaux lymphatiques qui se jettent dans les venules de la columelle tributaires elles-mêmes des veines auditives internes.

## ZUSAMMENFASSUNG

Die Makrophagen und die mit Plasma gefüllten Gefässe die im lockeren Bindegewebe des Modiolus enthalten sind zeigen dass hier die Zellzerfallsmassen und

## DURATION OF ANGULAR ACCELERATION AND OCULAR NYSTAGMUS FROM CAT AND MAN

### *II Responses from the Lateral Canals to Varied Stimulus Durations*

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A direct relationship between duration of acceleration and (a) decline of response during acceleration, (b) rate of decline of response after acceleration and (c) magnitude of secondary reaction is regarded as an indication of central process which limits a prolonged vestibular primary reaction. The process is manifested by its influence on relatively basic reflex reactions (nystagmus) in the cat and is more prominently manifested in man by its influence on sensory perception.

### INTRODUCTION

Ocular nystagmic responses elicited by angular acceleration have been found to be different in cat and in man (Collins & Guedry 1967). With prolonged stimuli (36 sec) a rise and decline of nystagmus during stimulation was obtained from cats for both lateral and vertical-canal stimulation. Human subjects did not exhibit a comparable decline during prolonged stimulation. Nystagmic reactions of the cat thus resembled the subjective (rather than the nystagmic) reactions of human subjects (Dodge 1923, Mittermaier & Rosenberg, 1956, Montandon & Fumeaux, 1957, Guedry & Caron, 1959, Elk, Jongkees & Klijn, 1960).

At least part of the difference noted above in regard to primary nystagmic reaction appears related to the prominent secondary nystagmus which characterizes responses of the cat to angular accelerations. Secondary nystagmus is opposite in direction to the primary response and it may reflect a process which develops during, and opposes continuation of the primary reaction.

The present investigation represents an extension of the earlier study (Collins & Guedry 1967). A range of stimulus durations was used to clarify relations between stimulus duration, the rate of decline of primary nystagmus, and the intensity of secondary nystagmus, and to compare further vestibular processes in cat and man.



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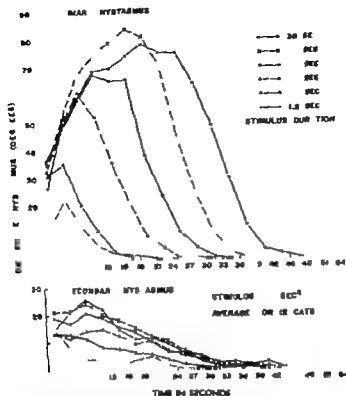


FIG. 1. Time-course plots of slow-phase eye displacement per 2-sec interval for 12 cats exposed to a stimulus duration of 4/sec<sup>2</sup> angular accelerations. For the 21 and 30 sec durations, responses reach peak and begin to decline during the stimulus. For the two briefest durations, the peak response occurs after stimulus termination. Peak magnitude of the secondary reaction appears related to stimulus duration.

each stimulus (a) to the end of the primary response and (b) to the start of the secondary nystagmus. The number of beats of primary nystagmus which followed stimulus termination was tabulated.

TABLE 1. Order of presentation of stimulus durations (in seconds)

Duration varied from 1.5 to 30 sec. All angular accelerations were 4/sec<sup>2</sup> and rotation was always counterclockwise. Only the lateral canals were stimulated.

Human subjects	Cat	Trials					
		1	2	3	4	5	6
T & Ch	109 & 109	1.2	3.0	9.0	15.0	21.0	30.0
Dj & Do	110 & 111	3.0	9.0	15.0	21.0	30.0	1.2
Se & Br	112 & 113	9.0	15.0	21.0	30.0	1.2	3.0
TA & Du	114 & 115	15.0	21.0	30.0	1.2	3.0	9.0
T & Pa	116 & 117	21.0	30.0	1.2	3.0	9.0	15.0
V & Pa	118 & 119	30.0	1.2	3.0	9.0	15.0	21.0

## METHODOLOGY

*Cats**Apparatus*

Rotational stimulation was provided in a light proof room with the Huffman Rotation Device (Collins & Huffman, 1964). Angular accelerations and decelerations were  $4/\text{sec}^2$  separated by 54 sec of constant velocity. Animals were tested in pairs (with their heads at the center of rotation) by means of a set of tethers (Collins & Updegraff 1966).

*Restraint*

Restraint was effected by the method of Henriksson, Fernández & Kohut (1961) and in the manner described elsewhere (Collins & Guedry 1967).

*Recording*

An Offner Type R Dynograph recorded horizontal components of eye movements from needle electrodes inserted by the outer canthi. A 3-sec time constant was used in amplification.

*Human Subjects**Apparatus*

A Stille-Werner RS-3 rotator was programmed to provide accelerations and decelerations of  $4/\text{sec}^2$  separated by 2 min of constant velocity.

*Recording*

An Offner Type T polygraph (time constant 3 sec) recorded horizontal components of eye movements from surface electrodes taped by the outer canthi.

*Procedure*

Each of 12 cats and 12 human subjects received 11 rotatory trials comprising  $4/\text{sec}^2$  accelerations and decelerations for 12, 30, 15, 21, and 30 sec. Rotation was always counterclockwise and the order of presentation of the stimulus durations was counterbalanced among pairs of subjects as indicated in Table 1.

None of the subjects had been used in previous vestibular experiments. Human subjects (6 men and 6 women) were instructed to signal onset and cessation of their rotatory experiences by means of a signal key.

*Scoring*

Slow phase displacement of the eyes was scored by measuring the peak to base-line distance for each beat of nystagmus and summing these values for 3-sec intervals. Time measurements were also made from the end of

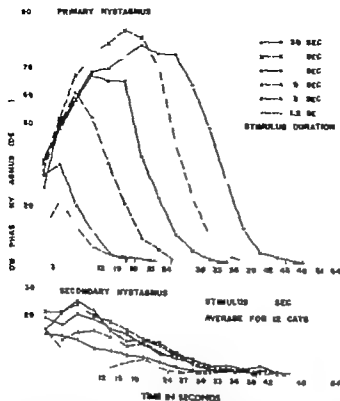


FIG. 1. Time-course plot of low-phase eye displacement per 2-sec interval for 12 cats exposed to 4 sec angular accelerations of 4/sec<sup>2</sup>. For the 30 and 15 sec durations, responses reach peak and begin to decline during the stimulus. For the two shorter durations, the peak response occurs after stimulus termination. Peak magnitude of the secondary reactions appears related to stimulus duration.

each stimulus (a) to the end of the primary response and (b) to the start of the secondary nystagmus. The number of beats of primary nystagmus which followed stimulus termination was tabulated.

TABLE 1. Order of presentation of stimulus durations (in seconds)

Durations varied from 1.2 to 30 sec. All angular accelerations were 4 sec<sup>2</sup> and rotation was always counterclockwise. Only the lateral canals were stimulated.

Human subject	Cats	Trials					
		1	2	3	4	5	6
Pr & Ch	108 & 109	1.2	3.0	9.0	15.0	31.0	30.0
Dy & De	110 & 111	3.0	9.0	15.0	21.0	30.0	1.2
En & Fr	112 & 113	9.0	15.0	21.0	30.0	1.2	3.0
Dr & Da	114 & 115	15.0	21.0	30.0	1.2	3.0	9.0
T & Ro	116 & 117	21.0	30.0	1.2	3.0	9.0	15.0
V & Pa	118 & 119	30.0	1.2	3.0	9.0	15.0	21.0

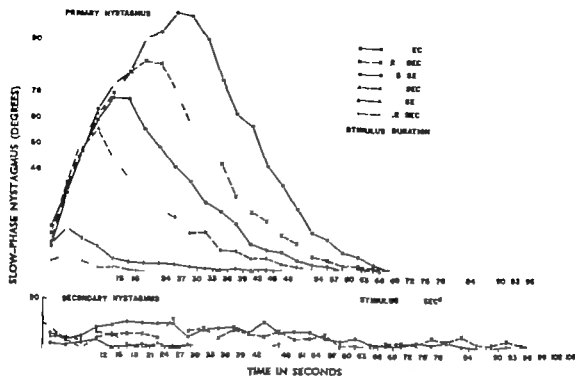


FIG. 2. Time-course plots of slow phase eye displacement per 3-sec interval for 12 human subjects exposed to 6 stimulus durations of  $\frac{1}{3}$ /sec<sup>2</sup> angular acceleration. No decline of nystagmus during stimulation is evident for any duration (compare with Fig. 1). Note that the peak response for the three shortest duration occurs after stimulus termination. No secondary responses were evident for the 1.2 and 3-sec stimuli and not all subjects showed secondary nystagmus for the longer stimuli.

## RESULTS AND DISCUSSION

### Cats

Measures of both response time and the number of beats of primary nystagmus following stimulus termination appear in Table 2. Post stimulus responses of greatest duration and magnitude occurred when stimulus durations were between 3 and 15 sec with the maximum post stimulus primary response occurring, in general, with stimuli of 9 sec duration.

The slow phase velocity of primary and secondary nystagmic responses was plotted for each of the 6 stimulus durations (Fig. 1). For the 21 and 30 sec stimuli there was a slight decline in response during constant angular acceleration. Consistent with data from cats in the earlier experiment (Collins & Guedry 1967) it appears that the nystagmic response reaches maximum intensity between 15 and 20 sec and declines after this, even though the stimulus is of constant magnitude and direction.

The peak magnitude of secondary nystagmus appears directly related to the duration of the angular acceleration. Secondary responses were obtained from all but one cat for the 6 stimulus-duration conditions; the exception (cat 112) gave no secondary nystagmus following the 1.2 second stimulus.

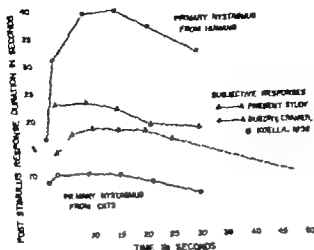


FIG. 3 Duration of the post-stimulus subjective and nystagmic reaction obtained in this study are compared with subjective data from an earlier study. The abscissa represents stimulus duration. Functions depicted for the two sets of subjective data and for primary (low-phase displacement) yul gms from cats are in close agreement.

### Human Subjects

Fig. 2 shows little or no decline in human nystagmus during constant angular acceleration irrespective of stimulus duration. This is consistent with human results of earlier studies (Collins & Guedry 1967, Collins & Guedry 1962, Guedry & Lauer 1961) but it is in contrast with results from cats in which nystagmus declined after about 20 sec of constant angular acceleration.

With brief stimuli (1.2 sec and 3 sec) it appears that in both man and cat the slow-phase velocity of nystagmus continues to increase ("overshoots") after the stimulus terminates (Figs. 1 and 2) whereas with prolonged stimuli, slow-phase velocity of nystagmus declines immediately after (in humans) or before (in cats) the stimulus terminates (Fig. 1).

As stimulus duration is increased up to about 15 seconds, the duration of the post-stimulus primary nystagmus increases. With longer stimuli, the duration of the post-stimulus primary response declines. In this respect human primary nystagmus corresponds fairly well in its temporal characteristics with the human subjective response. This is shown in Fig. 3 where the mean subjective turning scores from the present study are presented along with subjective data obtained in a previous study. In this earlier study (Guedry-Cramer & Koella, 1958) subjects had been trained in making subjective reports, whereas the present subjects had no preliminary practice. The rise and decline in duration of human nystagmus and subjective response as stimulus duration increases is also matched fairly

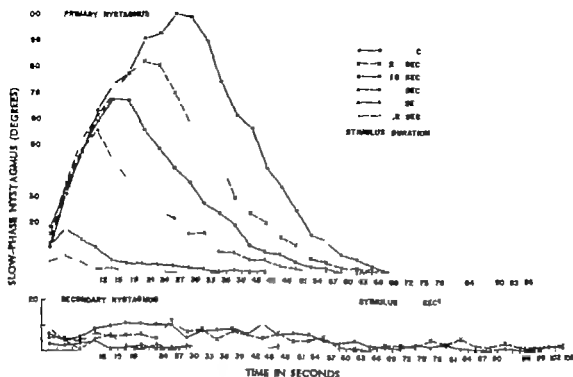


FIG. 2. Time-course plots of slow phase eye displacement per 3-sec interval for 12 human subjects exposed to 6 stimulus duration of 4/sec<sup>2</sup> angular acceleration. A decline of nystagmus during stimulation is evident for any duration (compare with Fig. 1). Note that the peak response for the three shortest durations occurs after stimulus termination. No secondary responses were evident for the 1.2 and 3-sec stimuli and not all subjects showed secondary nystagmus for the longer stimuli.

## RESULTS AND DISCUSSION

### Cats

Measures of both response time and the number of beats of primary nystagmus following stimulus termination appear in Table 2. Post stimulus responses of greatest duration and magnitude occurred when stimulus durations were between 3 and 15 sec with the maximum post stimulus primary response occurring, in general, with stimuli of 9 sec duration.

The slow phase velocity of primary and secondary nystagmic responses was plotted for each of the 6 stimulus durations (Fig. 1). For the 21 and 30 sec stimuli there was a slight decline in response during constant angular acceleration. Consistent with data from cats in the earlier experiment (Collins & Guedry 1967) it appears that the nystagmic response reaches maximum intensity between 15 and 20 sec and declines after this, even though the stimulus is of constant magnitude and direction.

The peak magnitude of secondary nystagmus appears directly related to the duration of the angular acceleration. Secondary responses were obtained from all but one cat for the 6 stimulus-duration conditions; the exception (cat 112) gave no secondary nystagmus following the 1.2 second stimulus.

TABLE 3 Measures of primary nystagmus following the termination of each rotatory stimulus for human subjects

Each response time is mean of responses to acceleration and deceleration stimuli. Stimuli were 4/sec<sup>2</sup> for 1.2, 3, 6, 15, 21, or 30 seconds.

Subject	1.2	3.0	6.0	15.0	21.0	30.0
Time from end of stimulus to end of primary nystagmus (sec)						
Pa	22.0	11.0	17.3	32.0	16.8	22.3
Da	12.6	25.2	42.4	34.1	61.6	45.3
Be	—	26.8	20.5	25.7	37.5	29.6
Do	18.3	19.6	36.9	51.3	36.3	29.8
Ch	13.1	25.1	40.0	33.0	24.5	23.9
Ro	13.6	41.3	28.4	34.9	41.2	40.3
V	10.9	62.2	44.0	41.3	38.4	37.9
T	—	20.9	42.6	26.7	33.1	27.2
De	31.8	42.0	44.4	48.4	40.1	35.7
Se	21.3	22.3	53.5	44.1	32.8	26.8
Pz	7.3	29.1	37.9	40.3	39.2	28.5
Dy	17.6	46.8	42.4	45.6	33.7	29.2
M	18.9	31.2	39.5	39.8	36.8	32.4

Time from end of stimulus to start of secondary nystagmus (sec)

Pa	—	—	—	—	—	26.1
Da	—	—	—	—	—	67.3
Be	—	—	—	—	—	—
Do	—	—	—	—	—	—
Ch	—	—	30.8	42.8	28.3	27.1
Ro	—	—	72.7	41.3	51.4	43.4
V	—	—	48.6	46.1	40.2	38.1
T	—	11.4	23.0	17.1	34.1	33.9
De	31.8	40.2	41.4	58.8	40.1	35.7
Se	21.3	—	—	32.3	32.9	26.8
De	—	—	37.7	41.6	39.3	33.5
Dy	—	—	50.4	60.0	33.7	31.9
M	( <sup>1</sup> )	( <sup>1</sup> )	48.6	41.3	37.5	37.2

Onset of primary nystagmus (sec end of stimulus)

Pa	12.0	12.0	19.3	38.3	38.0	27.5
Da	10.0	23.0	66.3	82.5	64.0	81.0
Be	—	27.0	11.5	29.0	33.0	29.5
Do	9.0	12.0	34.5	47.0	42.5	36.0
Ch	7.8	29.3	47.0	43.3	42.5	37.0
Ro	6.5	24.5	43.0	50.5	70.0	62.5
V	4.3	30.0	41.0	41.0	37.0	32.5
T	—	23.0	53.0	46.0	51.5	38.5
De	12.0	39.5	6.5	62.5	66.5	35.5
Se	39.0	31.5	78.5	73.0	52.5	54.0
Pz	4.0	12.0	34.5	34.0	24.5	34.0
Dy	13	29.5	47.0	61.0	48.5	42.5
M	10.1	24.5	41.7	50.3	48.7	41.7

Two few scores on which to base mean.



TABLE 2 *Measures of primary nystagmus following the termination of each rotatory stimulus for cats*

Each response value is a mean of response to an acceleration and a deceleration stimulus. Stimuli were 4/sec<sup>2</sup> for 1.2, 3, 9, 15, 21 or 30 seconds.

Cat	1.2	3.0	9.0	15.0	21.0	30.0
<i>Time from end of stimulus to end of primary nystagmus (sec)</i>						
108	10.9	12.4	14.6	10.6	8.1	6.0
109	5.9	8.3	8.2	5.4	4.0	1.6
110	18.5	7.3	9.2	12.0	5.0	2.3
111	7.1	11.1	8.8	6.5	4.3	.2
112	3.0	12.4	11.6	15.7	12.2	10.8
113	2.8	11.8	9.8	9.4	6.0	3.8
114	8.2	11.6	9.3	8.0	13.6	6.8
115	10.2	8.0	10.2	10.6	13.1	9.0
116	11.5	12.1	14.2	15.3	12.4	11.3
117	7.6	3.0	8.2	9.3	0.2	5.0
118	8.9	12.3	13.3	13.3	12.5	12.1
119	10.4	10.7	7.2	5.0	.2	2.5
<i>M</i>	8.8	10.1	10.4	10.1	8.7	0.5
<i>Time from end of stimulus to start of secondary nystagmus (sec)</i>						
108	15.6	15.4	20.8	15.6	14.5	13.2
109	7.0	18.9	13.5	9.9	6.5	6.2
110	15.9	6.6	12.9	6.0	9.4	6.7
111	15.0	10.8	12.6	10.8	7.5	10.6
112	—	14.6	17.5	24.4	20.1	18.1
113	15.7	18.3	14.1	11.6	9.0	7.5
114	12.5	12.7	14.7	25.4	15.1	15.6
115	17.3	19.5	14.6	16.7	15.0	14.0
116	13.0	10.9	21.3	17.5	15.1	16.1
117	11.2	18.0	14.8	12.6	13.0	15.6
118	9.3	16.3	15.3	15.5	10.4	15.7
119	15.2	14.9	11.8	11.4	9.5	1
<i>M</i>	13.6	15.6	15.3	14.9	12.6	12.2
<i>Beats / primary nystagmus after end of stimulus</i>						
108	4.0	12.0	10.0	12.5	11.5	6.5
109	1.5	7.0	9.0	6.5	2.5	1.0
110	3.0	3.0	6.5	6.5	4.0	3.0
111	2.5	7.0	8.5	7.0	4.0	0
112	2.5	8.0	11.0	18.5	16.5	9.5
113	2.0	7.5	9.5	9.0	5.0	3.0
114	5.5	8.5	12.0	7.5	17.0	5.5
115	4.5	7.0	8.5	9.5	16.5	10.5
116	5.5	8.0	16.0	18.0	9.5	18.5
117	4.0	5.0	—	8.5	3.0	12.0
118	12.0	15.5	17.0	19.5	19.0	15.0
119	4.0	8.0	5.5	4.5	0	1.5
<i>M</i>	4.1	8.0	11.1	10.6	9.8	7.3

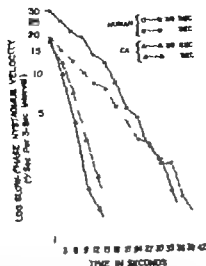


FIG. 1. Log plot of slow phase eye velocity following 15 stimulus durations for cat and human subjects. Data represent nystagmus measured from the point of stimulus termination and thus depict the rates of response decay. Decay is more rapid in cat and the longer stimulus duration produces more rapid declines.

If it is assumed that secondary nystagmus reflects a process which develops during the primary reaction and opposes its continuation, then all of the differences between man and cat may be due to this secondary process in cat having a more direct control of nystagmus than does its counterpart in man. The characteristics of subjective data reported by man resembled the alterations of nystagmus in cats during and after prolonged angular accelerations (Collins & Quedry 1967) and in some respects the nystagmus of man deviates from both the nystagmus of cat and the subjective responses of man during and after these unusual stimuli. It appears that the hypothesized secondary process exerts a control on man's sensory experience, i.e. the perceived angular velocity comparable to the control of nystagmus in the cat. This is not to say that the nystagmus of man is completely without the modulating influence of this secondary process because the rate of decline of both post-stimulus primary nystagmus and the occurrence of secondary nystagmus were influenced in man by the duration of the stimulus. However the control is apparently less consistent and hence probably less direct for the range of stimuli used in the present experiment. (Subsequent experiments have illustrated a pronounced secondary nystagmus in man when prolonged high-magnitude angular acceleration is used.)

It is parsimonious and reasonable to assume that a single process account for (a) the decline in response during prolonged angular acceleration, (b) the increased response decline following prolonged acceleration,

well by the change in temporal characteristics of nystagmus in the cat, also shown in Fig 3. Reference to Tables 2 and 3 shows that, in both man and cat, time elapsed from stimulus termination to onset of secondary nystagmus increases and declines in a manner which approximately parallels duration of the primary reaction.

Secondary nystagmus was not evident in the recordings of any of the human subjects for the 1.2 and 3 sec stimuli, and several subjects gave no secondary response to the 30 sec stimulus. However, frequency of occurrence of secondary nystagmus increased with stimulus duration and this may be interpreted as evidence for a relationship between stimulus duration and intensity of secondary response in humans similar to but more variable than that observed in the cat. In comparison with secondary nystagmus of the cat, the secondary nystagmus in man has a later onset, lower average intensity (relative to man's primary reaction) and seems to be more subject to individual differences.

Tables 2 and 3 suggest that the number of beats of secondary nystagmus is more closely related to the duration of primary post stimulus nystagmus than to the duration of the stimulus. This is in contrast to the maximum slow phase velocity of secondary nystagmus which seems related to the stimulus duration at least in the cat (see Fig 1). The decline in number of secondary beats with stimuli longer than 15 sec may signify an encroachment of the secondary reaction on the primary reaction.

Primary nystagmus in the cat is shorter in duration and has a lower beat frequency than that of man for the range of stimuli investigated. There is also a pronounced difference between man and cat in regard to the intensity ratio of secondary to primary nystagmus, the ratio being higher for the cat.

A log plot of nystagmus slow phase velocity with respect to time also shows the cat to have a substantially different rate of decline of nystagmus (lower time constant) than man for comparable stimuli (see Fig 4). It also appears that slope of nystagmus decline for both man and cat changes as a function of stimulus duration, the longer stimuli producing post stimulus nystagmus with a higher rate of decay (lower time constant).

### *General Discussion*

Because neurophysiological data from cats are sometimes applied to the explanation of reactions in man, it is important to compare the same response variables in men and cats exposed to identical vestibular stimuli. Nystagmus in cats declined during prolonged constant angular acceleration in spite of efforts to maintain alertness, whereas nystagmus in alert men did not decline during prolonged angular acceleration. The rate of decline of primary vestibular nystagmus following each stimulus was greater in cats than in man. The ratio of secondary to primary nystagmus was higher in cat than in man.

The conditions under which the "secondary processes" have been demonstrated, viz., prolonged constant angular acceleration, are seldom, if ever encountered in natural movement. Even a single, brief unidirectional angular acceleration followed by constant velocity does not occur in natural movement and, as noted in the present study intensity of nystagmus continues to increase briefly beyond the termination of short unidirectional stimuli. In natural movement, any brief angular acceleration is immediately followed by angular acceleration of opposite sign which returns the cupula toward its position of static equilibrium. Hence, in the case of either brief unidirectional stimuli or prolonged unidirectional stimuli, the vestibular reactions fail to follow the theoretical (Groen, 1960) cupula deflection. However this does not necessarily signify either an inadequate response system within the range of natural movements or a gross error in theoretical cupula mechanics. The departures from expected results signify a range of unnatural stimuli which are not accurately followed due to either inaccurate sensory detection or unfaithful central following of the input or both. Because the natural periods of movements of various animals are different (Melvill Jones & Spells, 1963) it is quite possible that the ranges of accurate sensory representation of movement, due to central and peripheral differences, will differ slightly in different animals.

The functional significance of the secondary process is not established. Some pathological conditions undoubtedly yield a central imbalance of spontaneous input from the two ears, and the "secondary process" may serve to readjust the point of homeostatic balance. Some complex motions of the head and body may terminate with minor residual cupula deflections, and this could require minor shifts in the point of balance between the two ears, which would be accomplished too slowly by the elasticity of the cupula. Tolerance to an increased level of vestibular stimulation en-

countered in land, sea and air travel may require a suppression at some level of vestibular inflow and it is possible that this secondary process serves this function. It has been shown that standard test stimuli administered as an angular acceleration are influenced in proportion to the duration of the preceding angular acceleration (Guedry, Cramer & Hoella, 1958) and it may be assumed that this finding is another manifestation of the "secondary process." Moreover with repetitive angular accelerations, the peaks of both primary and secondary nystagmus in cats diminish and shift toward earlier occurrences (Collins, 1964; Collins & Guedry 1967). This suggests that the secondary process encroaches more and more upon the primary reaction and thus limits the magnitude and duration of the primary reaction with repetitive stimulation. In humans, there are large individual differences in secondary nystagmus. If the secondary reaction is a manifestive process which serves to limit the primary reaction, it may prove to be an indicator among people with comparable histories of motion exposure of individual differences in ability to habituate to repetitive vestibular stimulation.

and (c) the increased secondary response following prolonged acceleration. The possibility that the cupula endolymph system is under-critically damped, contrary to the common supposition would explain a secondary response but this seems at variance with much of the evidence for the over-damped Torsion Pendulum analogy of van Egmond, Groen & Jongkees (1949) and could not explain findings (a) and (b). To explain these results on the basis of cupula deflection it would be necessary to assume that the stiffness of the cupula increases during prolonged constant angular acceleration. Van Egmond *et al* have proposed (1949) that events within the endorgan either bioelectric, biochemical or plastic change within the cupula, could account for secondary responses, and this possibility cannot be ruled out. Lowenstein (1950) has reported that increasing cupula deflection in elasmobranch initiates neural activity "in one after the other previously silent units" which often adapt themselves rapidly. Adrian (1943) and recently Melvill Jones (1967) recording from the vestibular nuclei in cats found little evidence for rapid adaptation. However Cappel (1966) has noted that slow declines in some units recorded in the vestibular nuclei of cats correspond temporally to declines in human subjective data. The possibility that there is a diminished sensory inflow during prolonged cupula deflection in cats remains open.

In man one aspect of the vestibular reaction (subjective velocity) declines while another aspect (nystagmus) does not decline during prolonged acceleration (Guedry & Lauver 1961). From this, it does not seem reasonable to attribute the decline of the one response to a suppression of sensory inflow. (Some reservations are necessary in this interpretation because average curves of different groups of subjects form the basis of the conclusion. Subjective and nystagmic data from the same subjects should be compared and studied for the presence of correlation.) Aschan & Bergstedt (1955) have evidence which implicates the central nervous system in secondary responses. Prolonged primary responses induced by unilateral caloric stimulation should provide an opportunity for adaptive changes within the cupula. Yet Aschan & Bergstedt (1955) reported little or no secondary nystagmus with unilateral caloric stimuli; whereas bilateral hot/cold caloric stimuli and rotational stimuli yielding primary responses of equivalent length, produced secondary responses.

Although secondary nystagmus (and apparently associated response modulation) in man and cat are probably attributable to the central nervous system, it remains quite possible that some of the differences between man and cat are attributable to differences in the properties of endorgans. e.g. the shorter primary nystagmic response in cats (irrespective of stimulus duration) is probably attributable to a greater cupula springaction in cat. Response parameters of the central nervous system may be conditioned or inherently matched to the response parameters of the cupula-endolymph system so that the shaping of responses to unusual stimuli may be similar in form but on a different time base in different animals.

The conditions under which the "secondary processes" have been demonstrated, viz., prolonged constant angular acceleration, are seldom, if ever encountered in natural movement. Even a single brief unidirectional angular acceleration followed by constant velocity does not occur in natural movement and, as noted in the present study intensity of nystagmus continues to increase briefly beyond the termination of short unidirectional stimuli. In natural movement, any brief angular acceleration is immediately followed by angular acceleration of opposite sign which returns the cupula toward its position of static equilibrium. Hence, in the case of either brief unidirectional stimuli or prolonged unidirectional stimuli, the vestibular reactions fail to follow the theoretical (Groen 1968) cupula deflection. However this does not necessarily signify either an inadequate response system within the range of natural movements or a gross error in theoretical cupula mechanics. The departures from expected results signify a range of unnatural stimuli which are not accurately followed due to either inaccurate sensory detection or unfaithful central following of the input or both. Because the natural periods of movements of various animals are different (Meivill Jones & Speils, 1963) it is quite possible that the ranges of accurate sensory representation of movement due to central and peripheral differences, will differ slightly in different animals.

The functional significance of the secondary process is not established. Some pathological conditions undoubtedly yield a central imbalance of spontaneous input from the two ears, and the "secondary process" may serve to readjust the point of homeostatic balance. Some complex motions of the head and body may terminate with minor residual cupula deflections, and this could require minor shifts in the point of balance between the two ears, which would be accomplished too slowly by the elasticity of the cupula. Tolerance to an increased level of vestibular stimulation encountered in land, sea, and air travel may require a suppression at some level of vestibular inflow and it is possible that this secondary process serves this function. It has been shown that standard test stimuli administered after an angular acceleration are influenced in proportion to the duration of the preceding angular acceleration (Guedry Cramer & Koella, 1958) and it may be assumed that this finding is another manifestation of the "secondary process." Moreover with repetitive angular accelerations, the peak of both primary and secondary nystagmus in cats diminish and shift toward earlier occurrences (Collins, 1964 Collins & Guedry 1967). This suggests that the secondary process encroaches more and more upon the primary reaction and thus limits the magnitude and duration of the primary reaction with repetitive stimulation. In humans, there are large individual differences in secondary nystagmus. If the secondary reaction is a manifestation of an adaptive process which serves to limit the primary reaction it may prove to be an indicator among people with comparable histories of motion exposure of individual differences in ability to habituate to repetitive vestibular stimulation.

## ACKNOWLEDGMENTS

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## RESUME

Un rapport direct entre la durée d'accélération et a) le déclin de réponse pendant l'accélération b) le cours de déclin de réponse après l'accélération et c) grandeur de la réaction secondaire est regardé comme indice d'un procédé central qui limite une réaction vestibulaire primaire prolongée. Ce procédé se manifeste par son influence sur des réactions réflexes relativement élémentaires (nystagmus) chez les chats et se manifeste d'une manière frappante chez les hommes par son influence sur la perception sensorielle.

## ZUSAMMENFASSUNG

Eine direkte Verwandtschaft zwischen Dauer der Beschleunigung und a) Verminderung der Reaktion während der Beschleunigung, b) Grad der Verminderung der Reaktion nach Beschleunigung und c) Ausmass der Sekundärreaktion werden als Zeichen eines zentralen Vorgangs, der eine andauernde vestibuläre Primärreaktion einschränkt betrachtet. Der Vorgang offenbart sich durch seine Einwirkung auf die verhältnismässig grundlegenden Reflexreaktionen (Nystagmus) der Katzen und ist bei Menschen durch seine Einwirkung auf die Sinneswahrnehmung mehr ausgeprägt.

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## RÉSUMÉ

Un rapport direct entre la durée d'accélération et a) le déclin de réponse pendant l'accélération, b) le cours de déclin de réponse après l'accélération, et c) grandeur de la réaction secondaire est regardé comme indice d'un procédé central qui limite une réaction vestibulaire primaire prolongée. Ce procédé se manifeste par son influence sur des réactions réflexes relativement élémentaires (nystagmus) chez les chats et se manifeste d'une manière frappante chez les hommes par son influence sur la perception sensorielle.

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1966) Such dimensional changes suggest a degree of local action of tones on the basilar membrane.

Electrophysiological studies especially with the method of cochlear potentials, also give indications of functional improvement of the auditory receptors in several species of lizards (Wever *et al.*, 1963) In many *Gekkonids*, for instance the sensitivity has reached a high degree over a wide range of tones and extends to the high tones, up to 10 kc/s. However the resemblance to the mammalian ear is not perfect in view of the non linearity observed by Wever and associates (1963, 1964) In several species Under normal conditions, in higher vertebrates, the cochlear potentials increase in amplitude as a linear function of sound intensity at higher sound levels they depart slowly from linearity and finally reach a maximum In most lizards this is not the case but the intensity functions show dips, plateaus, and irregularities that are difficult to interpret in terms of mammalian cochlear mechanisms.

In the present study the first goal is to describe the main aspects of the nonlinearity observed in the cochlear potentials. A second aim is to find some new indications of differentiated mechanisms in this ear

The Tokay gecko was chosen for these experiments because this species clearly shows the presence of nonlinear mechanisms and belongs to a family of lizards with one of the most highly developed inner ears The Tokay gecko has a relatively large number of hair cells, about 1500 and the basilar membrane on which the papilla rests has a tapered shape, being three times wider at the ventral than at the dorsal end (Wever 1966, Miller 1966)

## METHOD

### Subjects

In these experiments 36 Tokay geckos were used These specimens varied fairly greatly in size and weight. They measured over-all 26-48 cm, and 18-24 cm from snout to vent, and weighed 42-144 g. The sex of the subjects was not individually determined

### In situ

Animals in acute experiments were anesthetized with 5% or 10% Urethane (ethyl carbamate) in Ringer's solution, injected intraperitoneally The dose was 0.04 or 0.02 cc per gram of body weight, respectively Animal used in chronic experiments, in which the eighth nerve was sectioned or deafness produced by vertebrotony, were anesthetized with Nembutal (30 g/ml) using 0.06 cc per gram of body weight intraperitoneally and small doses were added during the experiment to maintain a deep level of anesthesia In some animals Flaxedil (Galamin triethiodide) in a dosage of 100 mg per cc was injected intravenously at a rate of about 0.5 cc per hour to cut off the activity of the middle ear muscles. In the

## PATTERNS IN THE COCHLEAR POTENTIALS OF THE TOKAY GECKO (*GEKKO GEKKO*)

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The nature and origin of the nonlinearity in the cochlear potentials of the lizard *Gekko gekko* are investigated. Potentials recorded from silver ball electrodes on the round window and in the cochlea are averaged in an on line computer and measured on a wave analyzer. The waveform of the potentials follows the frequency of the stimulating sound at low intensity and appears in general as a frequency doubling Fourier analysis of the potentials reveals a second harmonic that is often larger than the fundamental, depending on the frequency of the stimulating sound. Action potentials, middle ear structures, and middle ear muscles contribute to the distortion only to a small degree. This distortion must thus arise in the inner ear structures. Differences between potentials from two sites of recording support this hypothesis. The findings are analyzed in comparison with mammalian cochlear potentials and discussed in relation to anatomical characteristics of the auditory structures of the *Gekko gekko*.

### INTRODUCTION

Among the vertebrates, the reptiles are the first in the evolutionary scale that have an inner ear with a separate and well defined cochlear duct. In view of the close relation of the present day reptiles to the stem reptiles which gave rise to mammals and birds, this fact raises interesting questions of phylogenetic and physiological nature. The structure and function of the ear of reptiles have been the object of several studies in which one has looked for characteristics typical of a new step in evolution and with resemblance to the mammals.

Anatomical studies have disclosed a great diversity in the shape, the length and the detailed parts of the inner ear of reptiles, especially in the family of lizards. Indeed, cochlear structures of lizards can be extremely primitive or may show on the contrary some features of the mammalian cochlea, such as progressive changes in the dimensions of the basilar membrane and therefore in its mechanical properties (Wever 1963; Miller

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case the animals were tracheotomized and artificially respirationed. For these animals the electrocardiogram was monitored as an indication of the state of the animal.

In all experiments the body temperature was measured with a thermistor probe placed in the vent and it was kept constant at  $27 \pm 1^\circ \text{C}$  by a thermostatically controlled DC regulated heating pad.

### *Surgical procedure*

The surgery was performed under a binocular dissection microscope. Since in the lizards the middle ear cavity is part of the pharynx the round window was approached by an opening in the lower jaw close to the posterior end of the mandible. The hyoid bone was removed by careful dissection on one side except in chronic animals in which the opening was made as small as possible and the hyoid bone was spared to allow quick healing. The masseter muscles and the trachea were slightly retracted to facilitate the approach to the round window which was cleaned of all mucus.

In some animals in which intracochlear recordings were made a small opening was drilled in the lateral wall of the otic capsule, just ventral to the stapes, and a small bead electrode was introduced in it. Since the hole was tiny 0.27 mm in diameter very little perilymph escaped from the scala vestibuli.

### *Sound stimulation*

A general diagram of the stimulating and recording set up is shown in Fig. 1. The animal was placed in a sound insulated and electrically shielded room. The sounds were delivered to the drum membrane in a closed acoustic system that was sealed over the external auditory meatus with petroleum jelly or a ring of modeling clay.

The sound source was a Brüel and Kjær 1 inch microphone (type 4131) fixed to a plastic tube following the dimensions given by Ånggård (1965). A polarization voltage of 220 V DC was applied to the condenser microphone. The electrical sinusoidal signals were produced by a signal generator. They were accurately attenuated and amplified. A probe tube inserted in the center of the plastic sound tube led to a microphone in order to measure the sound pressure at the end of the sound tube close to the drum.

Most of the experiments were performed with continuous pure tones, but in some of them tone bursts were used by triggering the signal generator with pulses from a stimulator. In this case an onset generator producing a regular increase and decrease of the amplitude of the sinusoidal signals was introduced between the signal generator and the attenuators. Rise and fall times were generally 10 to 20 msec to avoid transients.

The frequency characteristics of the sound system were tested in a

range of the computer was extended by the use of a Northern Scientific type 303 micro-sampler which yields good resolution above 1000 c/s. The output of the computer was displayed on an X-Y plotter and on the face of an oscilloscope.

Cathode ray oscilloscope and computer were time locked to the sinusoidal stimulus by a triggering signal from the sinusoidal oscillator when continuous pure tones were used. When clicks or tones bursts were used, the triggering signal was provided by the stimulator.

## RESULTS

It is now generally accepted that the cochlear potentials are generated in the hair cells and that they play an important role in the early stage of sound perception. Therefore it was desirable in the Tokay gecko to analyze thoroughly the following main characteristics of these potentials: sensitivity to a large range of tone frequencies, waveform of the potentials, increase of amplitude following an increase of sound intensity, locus of distortion, and responses to transient sounds. The data gathered on these various points will be presented successively here.

### 1 Sensitivity

The sensitivity has been determined by presenting various tones at the sound pressure necessary to produce a response of 0.1  $\mu$ V RMS. When the ambient noise (noise in recording equipment and biological noise) was too high, values greater than 0.1  $\mu$ V were used as criterion. In such cases the sound pressures were calculated to indicate the level that would be necessary to produce a cochlear potential of 0.1  $\mu$ V. In the lizards an effort was made to use the technique which is common in mammals because of the nonlinearity appearing even at low intensities. Responses were obtained over a range from 100 c/s up to 8 kc/s in general, in some cases up to 10 kc/s. The sensitivity was measured for the whole range of frequencies only in a few cases, and most of the time only certain frequencies were chosen. For this reason the mean sensitivity curve (Fig. 4, Group II) displays for each frequency the average of groups with different numbers of subjects, varying from 2 to 21.

This mean sensitivity curve reveals some differences from the one published in five Tokay geckos by Wever and associates (1963) represented as Group I in Fig. 4. Although it is very similar in shape, the present subject shows a greater sensitivity than the previous ones without the sudden decrement around 1.5-2 kc/s. These differences can be explained by the ear given in this study: place the electrode on the round window membrane and not on the contiguous bone. The potentials were also picked up by an electrode of a slightly larger diameter to enlarge the surface of contact.

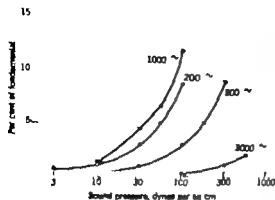


FIG. 2.

FIG. 2 Second harmonic distortion in the sound generating system.

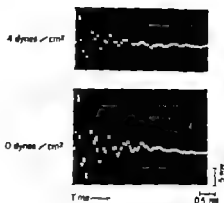


FIG. 3.

FIG. 3 Waveform of the rarefaction acoustic click for two levels of output. Negativity upward.

oscilloscope and the peak amplitude was measured. Owing to the excellent pulse response of the  $\frac{1}{4}$  inch microphone the peak sound level could be determined directly by using the calibration supplied with the microphone (Fig. 3). No wave differences (except inversion) were observed between condensation and rarefaction clicks. By increasing the intensity of the click or the duration of the electrical square wave changes in amplitude of the first peak occurred but not in the steepness of its slope.

### Recording

For the study of auditory functions by the method of cochlear potentials, a silver bead electrode, about 0.5 mm in diameter, was placed on the round window membrane. The potentials were picked up between this active electrode and a reference electrode clamped on the headholder. In some experiments the cochlear potentials were also picked up from the scala vestibuli at a point close to the stapes. In these cases silver bead electrodes of about 0.1 mm in diameter were used to fit a hole drilled in the lateral wall of the otic capsule.

As shown in Fig. 1 the potentials were amplified in a Tektronix 122 low level AC coupled, differential amplifier. The frequency response was limited to a band between 80 c/s and 10 kc/s. The signals were measured in a wave analyzer which acts as a selective voltmeter with a 3 cycles band width. The narrow band noise in the equipment as measured in the wave analyzer was normally 0.02  $\mu$  RMS with the input to the amplifier shunted with a 5 kilohm resistor.

Simultaneously the potentials were displayed in a cathode ray oscilloscope and fed into a Northern Scientific type 544 average response computer. The vertical output of the cathode ray oscilloscope was used for additional amplification of the signals to the computer. The frequency

range of the computer was extended by the use of a Northern Scientific type 303 micro-sampler which yields good resolution above 1000 c/s. The output of the computer was displayed on an X-Y plotter and on the face of an oscilloscope.

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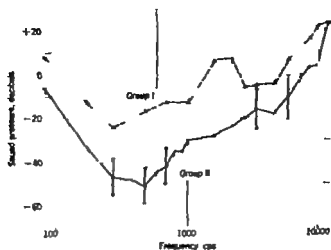


FIG 4 Mean sensitivity curves in two groups of *Gekko gekko* shown as the sound pressure in dB relative to 1 dyne/cm<sup>2</sup> required to produce a standard response of 0.1  $\mu$ V RMS. Vertical lines show the standard deviation, computed for points representing 10 or more measurements. The electrodes were all on the round window.

The possibility of electrical radiation from the sound source has been checked in animals in which the cochlea was no longer responding after injury to the blood supply to the cochlea. In these cases no signal could be detected from the round window membrane at sound pressures higher than those normally applied in the experiments.

Since the Tokay gecko like many other lizards can live for several days under Urethane anesthesia, experiments were often continued over at least two consecutive days. The sensitivity was checked each day and the variations never indicated a particular trend towards an increase or decrease of sensitivity. The variations rarely exceeded 10 dB.

## 2 Waveform

In mammals, a fundamental characteristic of the cochlear potentials is their sinusoidal form following the frequency of the stimulating sound. Only at high sound intensity do distortions appear. In the geckos the waveform of the cochlear potentials had not been studied in previous investigations for the reason that these potentials are very small and generally imbedded in the noise of the amplifier and of the cathode ray oscilloscope. In the present study with the aid of an average response computer which improves the signal-to-noise ratio the cochlear potentials could be differentiated from the noise.

In the Tokay gecko these averaged potentials had a sinusoidal form in agreement with the frequency of the stimulating tone only at low sound pressures and only for some frequencies (see Fig. 8 p. 14). Under most conditions these potentials appeared greatly distorted and often with a frequency double that of the applied tone. This type of distortion varies in degree from subject to subject but exists in all of them.

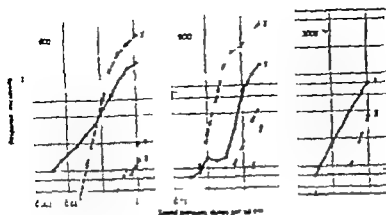


FIG. 5. Intensity function (in  $\mu$  RMS) and harmonic pattern for the cochlear potential to 3 pure tones. Each curve bears number indicating dB order in the harmonic series. Note the absence of 3rd and 4th harmonics for 3000  $\mu$ . Gecko: gecko D 6°.

In some geckos cochlear potentials were observed while the animals were dying and during the first hour after death, in order to follow their modifications. In these subjects death was caused by injecting a large dose of Flaxedil (Galamine triethylchloride) intravenously to stop breathing and heart beat, or by clamping the ascending aorta. Under these conditions the cochlear potentials decreased in amplitude after death, as has been shown in mammals (Davis *et al.*, 1934; Wever *et al.*, 1941) but the double-frequency wave form remained unchanged.

### 3. Intensity functions and distortion measurements

In order to obtain numerical values for the distortion in the ear the amplitude of the cochlear potential at the fundamental frequency and at its harmonic frequencies was measured as the sound was increased in steps of 5 or 10 dB. In Fig. 5 intensity functions are represented on a double logarithmic plot for three stimulating frequencies and their harmonics. From this figure it appears clearly that the increase of amplitude at the fundamental frequency bears no linear relation to the intensity of the stimulus, as had been found by Wever and collaborators (1962). This is in particular true for low frequencies while at higher ones (2 kc and above) a trend toward linearity exists.

Another important fact revealed in this figure is the large amplitude of the second harmonic at nearly all stimulating frequencies except the highest ones. The second harmonic appears sometimes at low levels of the sound stimulus, that is, at about the sound pressure required for a fundamental of 0.1  $\mu$ V or sometimes at 10 or 20 dB above this value. Its rise in magnitude bears generally a linear relationship to the sound pressure up to 1 dyne/cm<sup>2</sup>  $\pm$  10 dB then slowly departs from linearity. This second harmonic tends to reach and surpass in amplitude the component for the

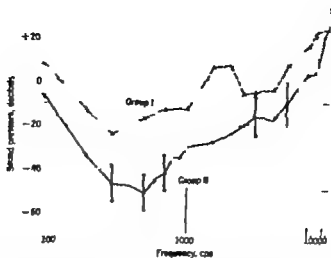


FIG. 4. Mean sensitivity curves in two groups of *Gekko gecko* shown as the sound pressure in dB relative to 1 dyne/cm<sup>2</sup> required to produce a standard response of 0.1  $\mu$  RMS. Vertical lines show the standard deviation, computed for points representing 10 or more measurements. The electrodes were all on the round window.

The possibility of electrical radiation from the sound source has been checked in animals in which the cochlea was no longer responding after injury to the blood supply to the cochlea. In these cases no signal could be detected from the round window membrane at sound pressures higher than those normally applied in the experiments.

Since the Tokay gecko like many other lizards, can live for several days under Urethane anesthesia, experiments were often continued over at least two consecutive days. The sensitivity was checked each day and the variations never indicated a particular trend towards an increase or decrease of sensitivity. The variations rarely exceeded 10 dB.

## 2. Waveform

In mammals, a fundamental characteristic of the cochlear potentials is their sinusoidal form, following the frequency of the stimulating sound. Only at high sound intensity do distortions appear. In the geckos the waveform of the cochlear potentials had not been studied in previous investigations for the reason that these potentials are very small and generally imbedded in the noise of the amplifier and of the cathode ray oscilloscope. In the present study with the aid of an average response computer which improves the signal-to-noise ratio the cochlear potentials could be differentiated from the noise.

In the Tokay gecko these averaged potentials had a sinusoidal form in agreement with the frequency of the stimulating tone only at low sound pressures and only for some frequencies (see Fig. 6 p. 14). Under most conditions these potentials appeared greatly distorted and often with a frequency double that of the applied tone. This type of distortion varies in degree from subject to subject but exists in all of them.

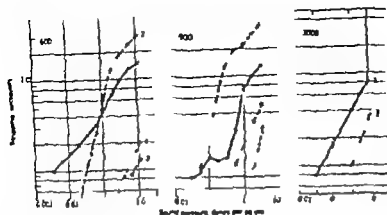


FIG. 3. Intensity function (1  $\mu$ V RMS) and harmonic pattern for the cochlear potential at 3 pure tones. Each curve bears number indicating its order in the harmonic series. Note the absence of 3rd and 4th harmonics for 3000 c/s. (G. H. G. 1967)

In some geckos cochlear potentials were observed while the animals were dying and during the first hour after death, in order to follow their modifications. In these subjects death was caused by injecting a large dose of Flaxedil (Galamine triethiodide) intravenously to stop breathing and heart beat, or by clamping the ascending aorta. Under these conditions the cochlear potentials decreased in amplitude after death, as has been shown in mammals (Davies *et al.* 1954; Weyer *et al.* 1961) but the double-frequency waveform remained unchanged.

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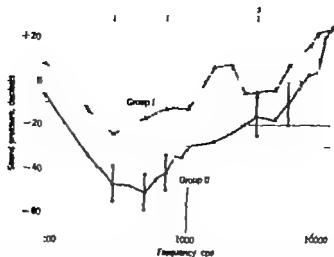


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### A. Contamination from the Nerve Action Potentials

It is known that in mammals the action potentials of the eighth nerve often occur during the positive half cycle of the cochlear potentials on the round window or when the cochlear potentials are going from negative to positive (Rosenblith & Rosenzweig, 1952; Leake & Kiang, 1962). Since the round window is as close to the fibers of the cochlear bundle as to the basilar papilla in the Tokay gecko, it is possible that nerve action potentials may be mixed with the cochlear responses and partly responsible for the strong second harmonic and for the double-frequency waveform observed.

To test this possibility an attempt was made to section the posterior branch of the eighth nerve in a fur animal. Six weeks after the surgery a control experiment was performed and the animal was then prepared for histological examination. In one case the section was successful, as could be judged from the responses to clicks (Fig. 6).

The cochlear potentials did not change in waveform except at 200 c/s and a quantitative analysis of the distortion did not reveal any improvement in linearity six weeks after the section. The only postdegenerative modifications speak in favor of an increase rather than a decrease of the amplitude of the second harmonic for all the frequencies, except for 200 c/s. These results correspond to mammalian studies in which the action potential contaminate only the low frequencies where a large number of nerve fibers can fire in synchrony with each wave of the sound stimulus (Rawdon Smith & Hawkins, 1939; Wolsk, 1963).

### B. Action of the Middle Ear Muscles

Weyer and associates (1961) found that in *Hemidactylus gecko* the lower part of the intensity function lost some of its irregularities after intraperitoneal injection of a curarizant (Intocetrin) to suppress muscle activity. However the slope of the intensity function failed to attain linearity under this condition. A moderate dose of Intocetrin was used by these authors to avoid a cessation of the respiration.

In order to understand accurately the role of the middle ear muscles in the irregularities of the intensity functions, muscle activity should be completely suppressed. For this reason these experiments were repeated with continuous intravenous injection of Flaxedil (Galamine triethylolide) on several animals that were artificially respired. It was generally assumed that the Flaxedil was acting when the respiration was noticeably slowed down or stopped altogether and when the natural rhythm no longer opposed the respirator.

Some results for one animal with 24 hours of continuous injection of Flaxedil are displayed in Fig. 7. The intensity functions for low and high frequencies tended to be more linear at low sound pressures, because of a

TABLE 1 *Second harmonic in per cent of the fundamental in the cochlear potentials recorded from the round window*

Means of 4 to 7 measurements.

Frequency (c/s)	Sound pressure in dynes/cm <sup>2</sup>				Remarks
	0.1	0.3	1	3	
200	85	183	285		} Great distortion
290	48	105	261		
400	283	137	426		
500	187	220	380		
600	138	265	190		
700	219	222	334		
800	209	379	676		} Extreme distortion
900	193	306	338		
1000	129	283	380		
1500	62	147	226		
2000		85	96		
3000		58	68	127	} Slight distortion
4000		22	41	100	
5000		58	51	167	
6000			34	77	

fundamental frequency Table 1 gives numerical values of the second harmonic expressed in per cent of the fundamental and shows clear differences between groups of frequencies: the distortion is much more pronounced for the middle than for the high tones.

Higher order harmonics appear at high sound pressures, that is, around 1 dyne/cm<sup>2</sup> and very often rise suddenly. Their slopes are steep and their amplitudes remain smaller than the fundamental. They behave as would be expected from the mammalian studies on distortion: very differently from the behavior of the second harmonic in the gecko. At frequencies higher than 1500 c/s, these harmonics are very small or unmeasurable at the sound pressures applied in these experiments.

These observations lead to the conclusion that the nonlinearity of the cochlear potentials in the Tokay gecko is produced by the generation of a strong second harmonic, which does not seem to belong to the distortion pattern described in various higher vertebrates (Wever & Lawrence 1954).

#### 4 Origin of the distortion

The next step of this study was to investigate the origin of this double frequency or strong second harmonic. The following possibilities were considered: contamination of the cochlear potentials by neural action potentials; action of middle ear muscles; the role of the middle ear structures in sound transmission; and distortion generated in the inner ear.

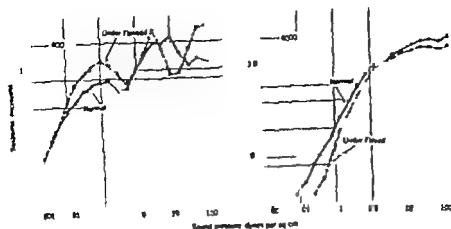


Fig. 7 Effect of curarization on intensity functions (I  $\mu$  RMS) of two tones. (G Eke geck D 21)

monic were taken in these experiments for methodological and technical reasons.

In these experiments, although the doses of Flaxedil were so large that in mammals they would have suppressed muscle activity totally (Wersäll, 1958) irregularities were still observed in the cochlear potentials. This fact suggests that the middle ear muscles are not responsible for the nonlinearity.

### C. Role of the Middle Ear in the Transmission of Sound

The middle ear as a locus of production of harmonic distortions has been excluded in mammals on the basis of a number of experiments (Weyer *et al* 1938, 1940-1941; von Békésy 1960a). In most lizards the middle ear consists of two parts: the cartilaginous extracolumella and the bony columella ending in a footplate in the oval window. Because the pattern of distortion in the Tokay gecko is very different from that in mammals, the question arose whether the very simple and primitive ossicular system could account for the nonlinearly observed. Two experiments were performed to investigate this problem.

(a) After recording the amplitude of the fundamental and second harmonic under normal conditions, the columella was sectioned first, then the drum and ossicles were removed. After each step of the surgery measurements of cochlear responses were repeated. They did not show any important modifications, either in linearity or in distortion pattern when the decrease in sensitivity was compensated for by increasing the stimulus intensity.

(b) In the second experiment, after the usual measurement of sensitivity and determination of the intensity functions, the drum and columella



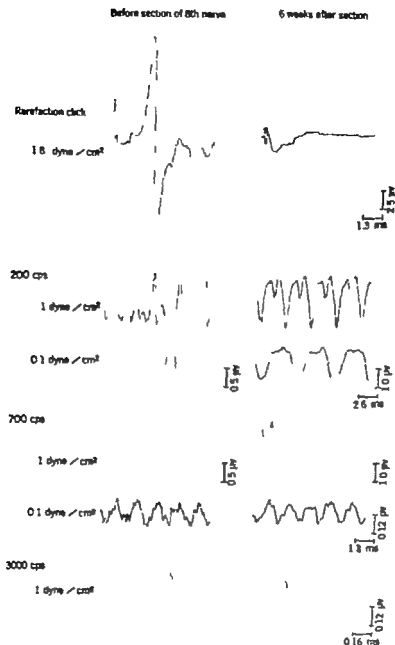


FIG. 6. Waveforms (averaged) of the cochlea potential and of the response to clicks before and after 6 weeks of degeneration. Amplitude  $\mu$  = peak-to-peak stimulation artifact (*Geck gekk* D 49).

reduction of the biological noise which allows more reliable measurements. However, for 400 c/s (and also other frequencies) there was a bending over of the curve at 0.1 dyne/cm<sup>2</sup> followed by a second increase of amplitude that was not suppressed by curarization. Such a function is still difficult to explain: if the first bending represents a real maximum, a further increase of the sound pressure should produce impairment of the hair cells and loss of sensitivity (Wever & Lawrence 1944). This was not the case here and even after greater sound pressures were applied the measurements could be immediately reproduced. No readings of the second har-

this impedance is not known the two sets of results can only be compared in terms of cochlear potential.

At low frequencies the results do not show great differences between measurements with the middle ear intact and those with vibration of the footplate. From 1000 c/s upward the second harmonic is always present but is much smaller for mechanical vibration than for air-borne sounds. More information is still needed to account for this phenomenon which may be related to the coupling of the vibrator to the mechanical system of the ear as well as to characteristics of the ossicular chain.

#### D. Origin of the Distortion in the Inner Ear

Since the irregularities and nonlinearity of the intensity functions are due only in minor degree to a contamination by nerve potentials, to the activity of the middle ear muscles, and to the behavior of the middle ear system, the strong second harmonic must arise in the structures of the otic capsule, probably in the cochlear duct.

This hypothesis was supported by recordings from different locations in the cochlea. In three animals the cochlear potentials were recorded simultaneously from electrodes on the round window and in the scala vestibuli, ventral to the footplate of the columella. Systematic differences in sensitivity, frequency range and amount of distortion were observed in these experiments.

The differences in sensitivity are shown in Fig. 9. For all low tones, less sound pressure was needed to record responses of standard amplitude from the scala vestibuli. At high frequencies, on the contrary, the sound intensity had to be increased in order to get the standard cochlear potential.

The potentials from the scala vestibuli were much more sinusoidal in shape than those from the round window. Only at higher levels of sound about 1 dyne/cm<sup>2</sup> distortion appeared and it never became severe enough to give the appearance of a frequency doubling.

The intensity functions measured from the scala vestibuli also appeared much more regular and linear. The maximums were larger except for frequencies above 2 kc/s. The harmonic pattern resembles that of mammals, since the second harmonic appears only at higher levels of sound, grows linearly and reaches a maximum which is always smaller than that of the fundamental (Table 2).

Differences of phase were observed between the signal recorded from the round window and those from the scala vestibuli. Under the conditions of these experiments, the phase difference was generally smaller than 180 degrees and varied with frequency and intensity.

To summarize the differences described are important from several points of view. Possible variations in impedance of the two recording sites can account for some of them, such as the differences in sensitivity. However, in the recordings from the scala vestibuli the large differences in

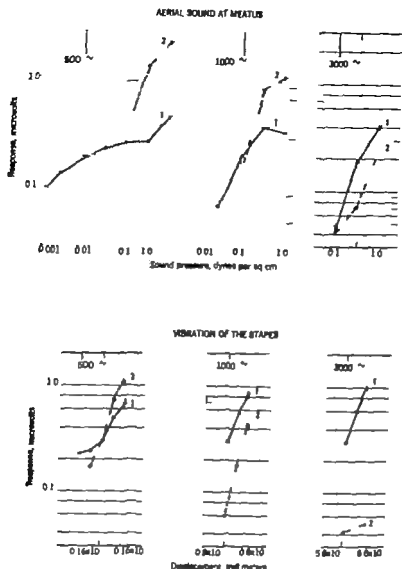


FIG 8. Intensity function (in  $\mu\text{V RMS}$ ) of cochlear responses to tones of different frequencies with aerial sound applied to the external auditory meatus and with vibration of the stapes: (1) Fundamental (2) 2nd harmonic (G LA 9 K D 60)

were again removed up to the footplate of the columella. The footplate was vibrated with a Goodman vibrator which had been thoroughly shielded and checked for electrical radiation. The displacement amplitude of the vibrator was measured optically with an MTE Photonic Sensor. The amplitude of the vibration was increased until a reading corresponding to a previous measurement of the cochlear potentials was reached. From there on the amplitude was increased in 5 or 10 dB steps and the waveform was displayed on the computer. In Fig 8 the magnitude of the cochlear potentials is shown in microvolts as a function of sound pressure and also as a function of the vibratory displacement of the footplate. Because the displacements of the drum membrane and the columella under the action of sound pressure depend upon the impedance of the mechanism and since

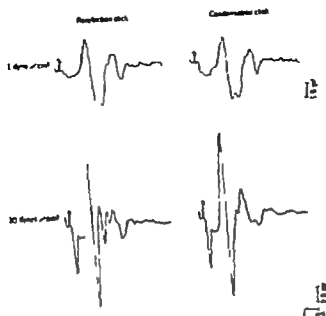


FIG. 10. Averaged responses to condensation and rarefaction clicks, recorded from the round window. Amplitude in  $\mu$  peak-to-peak. Repetition rate 1 sec (Gekk gecko D 63).

ward movement of the drum and conversely it is negative for a condensation click.

In the Tokay gecko, both condensation and rarefaction clicks produce a positive potential on the round window followed by a large negative-to-positive action potential, as shown in Fig. 10. This positive potential which remains after sectioning of the eighth nerve increases in amplitude in a linear relation to the intensity of the clicks, becomes sharper and narrower and assumes the form of a spike at high intensity. Its latency (taken as the delay between the stimulus artefact and the foot of the wave) varies from 0.4 msec around 1 dyne/cm<sup>2</sup> to 0.13 msec at 10 dynes/cm<sup>2</sup>. No systematic differences appear between the latency of the responses to condensation and rarefaction clicks.

This positive potential changes to negative when it is picked up from the scala vestibuli. This corresponds to the reversal of polarity already observed in the potential with pure tone stimuli, and well known in mammals (Tasaki *et al.*, 1962).

#### DISCUSSION

Concerning the nonlinearity observed by Wever and associates in the cochlear potential of the Tokay gecko, the present study has disclosed four main points which may lead to an explanation of this phenomenon.

First, in responses to pure tone stimulation an important distortion exists

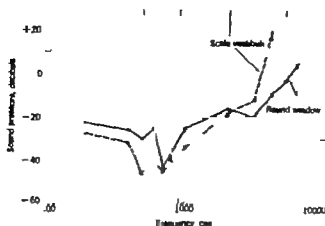


FIG. 9 Sensitivity curves from two recording sites. (*Gekko gecko* D 47)

sensitivity for the high and low frequencies raise the question whether this electrode may be in a favorable position to pick up the activity of a structure especially tuned for low tones, either the more ventral part of the basilar papilla or the lagena macula.

### 5 Responses to transients

In mammals it has been shown that a transient sound such as a click produces a train of electrical waves (Rosenblith & Rosenzweig, 1952; Peake & Kiang 1962). In recording from the round window the first wave is positive in the case of a rarefaction click which produces an out

TABLE 2 Amount of second harmonic in per cent of the fundamental for the cochlear potentials recorded from the round window and from the scala vestibuli for various tones and sound pressures (*Gekko gecko* D 4)

Frequency (c/s)	Sound pressure in dynes/cm				
	0.03	0.1	0.3	1	3
400					
Round window		0	35	276	
Scala vestibuli		0	9	30	
600					
Round window	0	160	400	255	
Scala vestibuli	0	34	57	56	
1000					
Round window	0	33	103	440	
Scala vestibuli		0	26	65	
4000					
Round window				39	46
Scala vestibuli					100

results obtained for very low intensities under Flaxedil which greatly reduced the biological noise. However two facts cannot fit into this framework. First it is impossible to assimilate the pattern of distortion measured in geckos to that obtained in mammals. The existence of a strong second harmonic which is much larger than the fundamental, seems to belong specifically to the inner ear of the Tokay gecko and perhaps other lizards. Secondly it was possible to increase the sound intensity after having reached the overloading region and still record a new increase of amplitude without producing any temporary or permanent threshold shift indicative of damage as would always occur in mammals.

Unless the mechanisms of harmonic distortion differ in the lizard's cochlea from that of mammals, it seems that the distortion hypothesis may account only for a small part of the action peculiar to this ear.

## 2. Two-structural Hypothesis

According to the observations on the anatomy of the cochlear duct and the morphology of the basilar papilla in the Tokay gecko, it may well be that cochlear responses measured at the round window are the sum of potentials arising in two different populations of hair cells. The possible realizations of this mechanism will be described and their functional roles discussed.

### (a) Effect of Intensity on receptor response

In the organ of Corti of mammals, greater sensitivity has been attributed to the outer hair cells than to the inner ones, on the basis of their position on the basilar membrane, their attachment to the tectorial membrane and their susceptibility to injury (Davis *et al.* 1952, 1958; von Békésy 1960a).

In the Tokay gecko the distinction between inner and outer hair cells does not exist, but hair cells differ in their relation to the tectorial membrane (Fig. 11). The cells attached to it by means of fiber connection and finger-like processes, which act as a restraint and tension on them, may be readily stimulated at low intensities. On the contrary the other group of cells connected to the sallet may be stimulated only at high intensities, since this structure is nearly independent of the tectorial membrane and acts only through its own inertia. A certain time delay and phase shift may also exist between the stimulation by the "sallet" and by the finger-like processes (Wever 1960).

The present study has demonstrated that the cochlear potential generally has a normal waveform at low intensities which probably reflect only the activity of one group of hair cells. The strong second harmonic which appears at slightly higher sound levels might then be due to the simultaneous action of two groups of hair cells, the first one acting nonlinearly and the other still linear but with phase shift. The fact that

in the cochlear potentials, especially a large second harmonic which sometimes exceeds the fundamental component

Secondly since the sound source the middle ear and the nerve activity can be largely excluded as the origin of the distortion the structures of the inner ear may be considered as the principal source

Thirdly the pattern of cochlear responses to sound varies within the cochlea according to the location of the active electrode relative to the inner ear structures

Finally an unusual feature has been noticed in the responses to clicks, which induce a positive potential on the round window regardless of the polarity of the click

These four points show that the function of the ear of the Tokay gecko differs in many aspects from that of higher vertebrates. In mammals and birds indeed it is well known that the cochlear potentials at ordinary levels reproduce the waveform of the stimulus. Only at high levels of sound does harmonic distortion appear and the waveform of the potential is somewhat altered as overloading occurs. At the highest sound levels the total overtone content represents only a little more than 50% of the size of the fundamental. In response to transient stimuli the receptor potentials recorded from the round window are always positive with an outward movement of the drum and negative with an inward movement.

Although no full explanation of the special cochlear patterns of the Tokay gecko can be given at this time, it is possible to formulate several hypotheses about the possible mechanisms in this ear in relating functional observations with anatomical structures and their characteristics. Among these hypotheses, two will be discussed here. The first relates the existence of the distortion to the small number of hair cells. The second examines the possibilities of two structures reacting to sound stimulation.

### 1 Distortion

According to the volley theory (Wever 1949; Wever & Lawrence 1954) each tone has a wide operating area on the basilar membrane with a site of maximal stimulation. When the increasing sound pressure reaches a certain level the action of the hair cells becomes nonlinear first at the site of maximal stimulation and then around it. If the sound is increased beyond the overloading point, irreversible injuries occur.

The basilar papilla of the Tokay gecko has in comparison to mammals a very small number of hair cells. This implies that this structure may function with a linear relationship to sound pressure only at low levels of stimulation. Most of the linear portion of the intensity curves would be below cochlear potentials of 0.1  $\mu$ V amplitude and lost in the general noise. Therefore at the levels of sound used in the present experiments potentials should be extremely distorted and close to overloading.

Some data seem to confirm this hypothesis, namely the more linear

results obtained for very low intensities under Flaxedil which greatly reduced the biological noise. However two facts cannot fit into this framework. First it is impossible to assimilate the pattern of distortion measured in geckos to that obtained in mammals. The existence of a strong second harmonic which is much larger than the fundamental, seems to belong specifically to the inner ear of the Tokay gecko and perhaps of other lizards. Secondly it was possible to increase the sound intensity after having reached the overloading region and still record a new increase of amplitude without provoking any temporary or permanent threshold shift indicative of damage as would always occur in mammals.

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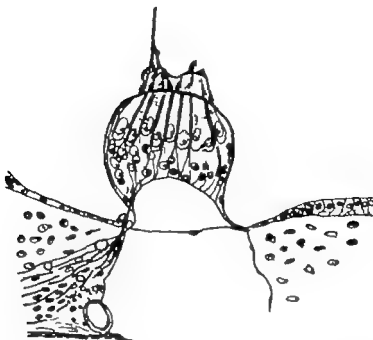


FIG. 11 The auditory papilla of the *Gekko gekko* from near the middle of the cochlea, 1100 microns from the dorsal end. Note the existence of two connections to the tectorial membrane: the finger-like process and the sallet. Scale  $\times 500$ . (From Weyer 1963.)

responses to high frequency tones do not show as great an amount of distortion speaks in favor of this hypothesis, since the "sallet" is located only in the more ventral half of the basilar papilla where low tones are expected to act specifically.

Some experiments on the activity of the eighth nerve which will be reported in another paper (Hepp-Reymond, 1968) give further data supporting this hypothesis. Histological and electrophysiological results on some overstimulated geckos and data gathered on other species of lizards without the different kinds of tectorial attachment will be of help in testing this hypothesis.

#### (b) Directional sensitivity of receptors

In several structures of the acoustico-lateralis system as the lateral line organs, the utricular macula, and the saccular macula, there have been recordings of double-frequency microphonic potentials and of two groups of fibers that discharge during opposite phases of sound or vibration (de Vries & Bleeker 1940; Juelof *et al.* 1952; Kuiper 1956; Flock 1965).

These electrophysiological results were related to electronmicroscopical observations, according to which each hair cell is morphologically polarized by the presence of a kinocillum at the periphery of the sensory hair bundle. Adjacent hair cells may have kinocilia pointing in opposite direction as has been shown in the lateral line organs. Therefore under sinusoidal stimulation some cells will be depolarized and some hyperpolarized. In a model developed by Flock (1965) depolarization should be always larger

than hyperpolarization to explain double-frequency potential. This has been proved by the fact that in response to transient stimuli negative potentials were always evoked at the receptors regardless of the polarity of the transient pulse.

In the inner ear of the Tokay gecko, the presence of double-frequency potential and the existence of positive potential in the round window in response to clicks of opposite polarity show good resemblance to some of the functional properties of the mammalian labyrinth. Directional sensitivity defined as differential function of the direction of the displacement is very important in labyrinthine function but it seems of no use in hearing and it is difficult to imagine that the basilar papilla would act in this way. Nevertheless the structure of the hair tuft of the Tokay gecko as shown by Wever (1962) reveals some morphological polarization (Fig. 11). Since the hairs increase in size irregularly, sometimes toward the lateral side sometimes to the medial wall of the cochlear duct. Recent results in electron microscopy of the basilar papilla of the *Certhronotus multifloratus* (Mulroy) reveal the existence of a kinocilium on each hair cell. On a group of cells appears to be morphologically polarized in one direction, and another group in the opposite direction. Wever and Mulroy's findings lead to the reflection that the basilar papilla, which is said to arise from the same structures as the lateral line organs, can still have some remnant of primitive morphological character that are responsible for the receptors observed. In this case one can wonder what geckos are able to hear.

#### Contaminating potential from the lagenar macula

Another speculative explanation of double-frequency potential invokes the possible role of the lagenar macula. This otolithic structure which is well situated in the cochlear duct resembles the utricular macula. In lizard it is quite large, decreases then in bird, and no longer exists in mammals. In geckos it is greatly extended, especially at the ventral end of the cochlear duct, as the studies of Hamilton (1960) and of Miller (1966) have shown. Nothing is really known about this sensory epithelium to which in fishes has been attributed directional sensitivity (Lewin & Roberts, 1950) in birds vestibular functions (Schwartzkopff, 1949) and in lizard auditory functions (Beccari, 1952; Hamilton, 1963). It may well be that the cells of this macula react to the direction of the displacements of the endolymph by producing microphonic potential that contaminate the recordings from the basilar papilla.

Concerning the differentiation of the ear of the Tokay gecko, in terms of local action of the tones on the basilar membrane as in mammals, the present study cannot bring a definitive answer but describes some phenomena which strongly support this hypothesis.

Obvious differences in the cochlear patterns for low and high tones have

been observed in all experiments. In particular the second harmonic is much more prominent in responses to low tones up to 1500 c/s (see Table 1). This fact speaks in favor of some differences in the transformation of energy of various groups of tones, which may be related to the fine structure of the basilar papilla. In mammals it has been demonstrated that the low tones are more strongly located in the part of the basilar membrane which is less stiff and has a greater mass that is near the apex of the cochlea. By extrapolation Wever suggested that in geckos the most favorable place of action for the low tones on the basilar membrane should be the ventral end and for the high ones the dorsal part which is narrower and has less mass.

In the discussion on the nonlinearity of the cochlear potentials, it was suggested that it might be explained by the interaction between the activity of two structures. From Wever's studies it is clear that finger like processes and sallets act on two different groups of hair cells at one level of the basilar papilla, that is in the ventral half. On the contrary, in the dorsal region all the hair tufts are connected to the tectorial membrane in a similar way through fiber connections or finger like processes. Therefore if the low frequency tones have their sites of maximal stimulation in the ventral part of the basilar membrane and if the sallets (along with the finger like processes) are in the region of the generation of the strong second harmonic, it might be expected that responses to low tones will contain a great amount of distortion. High frequency responses would then appear quite linear as in the mammalian ear.

The good correspondence of the anatomical observations with electrophysiological findings supports not only the double structure hypothesis but also the theory that different frequencies have specific loci of action on the basilar membrane. This suggests that the place principle in hearing appears in the cochlea of some lizard species.

*In conclusion* the results of the present study reveal some complex problems that are far from being solved. Electrophysiological investigations of eighth nerve activity, selective lesions in the cochlear duct, more detailed anatomical data and behavioral studies are still needed before an understanding of the auditory capabilities of the geckos will be reached. It seems that the ear of the Tokay gecko is not as simple as formerly believed and cannot serve as a simple model for the mammalian auditory organ, albeit there are many structural similarities in the differentiation of the receptors.

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# A STUDY ON THE BIOPHYSICAL CHARACTERISTICS OF THE CAT LABYRINTH

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An investigation was made of the biophysical dimensions of the cat labyrinth. In each semicircular canal the diameter of both membranous and osseous canal and the radius of curvature were measured. From these measurements the length of the canal and its volume were calculated. The volume of sacculus, utricle, endolymph and perilymph were also calculated after measuring the area in histological serial sections. Distances between canals were also measured and the angles between them were determined. The data were used for calculating the constant of the fundamental differential equation of the cupula-endolymph system.

## INTRODUCTION

The fact that most of our experimental work is carried out in the cat and that the biometric data on its vestibular sense organ are incomplete prompted the investigation reported here. The aim was to determine accurately the following parameters: cross-sectional radius of each semicircular canal and its radius of curvature, the length of each canal, the distances and angles between them and finally some dimension of their cellular structures including their volume. Perhaps these analytical data may facilitate the understanding of the physical model of the cupula-endolymph system and the action of vestibular stimulation such as that produced by Coriolis forces upon the sense organ of the cat.

## THEORETICAL CONSIDERATIONS

The physical model of the cupula-endolymph mechanism as postulated by Lorentz de N6 (1927-1934), Steinhausen (1933), van Egmond, Cruen & Jongkees (1949) and others have been considered in our work.

It appears that during excitation as postulated by Jones & Spill (1963) the sluggishness of head movements associated with increases in animal

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$$H = 8\pi^2\eta R^2 \quad (6)$$

Therefore 
$$\beta_{\text{min}} = \gamma_{\text{min}} \frac{R}{4\eta} r^2 \quad (7)$$

or 
$$t_{\text{min}} = \frac{4\eta \beta_{\text{min}}}{\omega^2 r} \quad (8)$$

Equation (8) shows that for a given angular acceleration,  $\omega$ , the speed of the response  $t_{\text{min}}$  is a function of both threshold  $\beta_{\text{min}}$  and  $r$ . Since the speed of the response in a sensory organ is one parameter of its sensitivity we may define the sensitivity  $S$  of a semicircular canal as,

$$S = \frac{1}{t_{\text{min}}} \quad (9)$$

indicating that the shorter is  $t_{\text{min}}$  the higher the canal sensitivity. Then

$$S = \frac{\omega^2 r^2}{4\eta \beta_{\text{min}}} \quad (10)$$

This equation expresses that the sensitivity of the semicircular canal is proportional to the square of its internal radius,  $r$ , as postulated by Jones & Spells (1963).

The theoretical considerations for the postulate that the time constant of the cupular return is a function of  $H$  are the following.

The return angular movement of the cupula after reaching a displacement  $\beta_0$  is

$$\beta = \beta_0 e^{-\frac{t}{\tau}} \quad (11)$$

The time constant is,

$$\tau = \frac{H}{\Delta} \quad (12)$$

The stiffness coefficient,  $\Delta$ , of the cupula can be obtained from

$$\Delta = \pi \mu r^2 R \quad (13)$$

( $\mu$  = pressure exerted by the cupula per unit angular deflection). Therefore

$$\tau = \frac{8H\eta R}{\mu r^2} \quad (14)$$

Equation (14) shows, as claimed by Jones & Spells (1963) that the time constant (the cupular return) is a function of the ratio  $H^2/r^2$ . This ratio fulfilled the requirement of their theory that an increase in sensitivity matching the slower head movements of large animals must be associated with a corresponding increase in the time constant of the cupula return.



size was compensated by adapting the canal sensitivity and the time constant of cupula return. They predicted according to Steinhausen's theory of the cupula-endolymph mechanism that changes in the body mass ( $m$ ) are associated with a proportional change in both the cross section radius,  $r$  and the radius of curvature,  $R$ . After statistical analysis of these dimensions in a number of species they postulated that the relation between  $r$  or  $R$  and  $m$  could be expressed in the following equation

$$\log_{10} 100r^2 \text{ (or } \log_{10} 100R) = n \log_{10} m + A \quad (1)$$

where  $m$  is in kg,  $r$  and  $R$  in mm and  $n$  and  $A$  are constants.

From theoretical considerations and actual measurements of  $r$  and  $R$  Jones & Spells (1963) concluded that the sensitivity is dependent on  $r$  while the corresponding change in the time constant of the cupular return is dependent on  $R$ .

The hypothesis of Jones & Spells (1963) on the adaptation of the semicircular canals to dynamic requirements of the species was later expanded by Mayne (1965). He postulated that the matching of the semicircular canals to the requirements imposed by changes in body mass depend on the range of frequency response and resolution of the system. Mayne indicated that the matching is accomplished by five parameters, that is, radius of membranous canal, radius of its curvature, volume of the ampulla, stiffness of the cupula and number of sensory cells in the crista.

The relation between  $r$  and sensitivity of the semicircular canal is expressed in the following considerations. The threshold of excitation  $\beta_{\min}$  postulated by theoretical developments (van Egmond, Groen & Jongkees, 1949; Groen, 1956, 1957) is reached at a certain angular displacement of the cupula  $\beta_{\min}$ . This minimal value depends on the ratio of endolymph moment of inertia  $\Theta$  to the moment of friction per unit angular velocity  $\Pi$  times the so-called "minimum impulse"  $\gamma_{\min}$  that is

$$\beta_{\min} = \gamma_{\min} \frac{\Theta}{\Pi} \quad (2)$$

where  $\gamma_{\min} = \dot{\omega} t_{\min}$  (Mulder's law) (3)

where  $\dot{\omega} = d\omega/dt$  ( $\omega$  angular velocity of rotating device)

$$\Theta \approx 2\tau^2 \rho r^2 R^3 \quad (4)$$

( $\rho$  density of endolymph)

$$\Pi = 8\eta\pi R^2 L \quad (5)$$

( $\eta$  viscosity of endolymph,  $L$  length of canal)

We would like to point out that if the semicircular canal is considered as a complete ring (toroid) then  $\Theta$  is exactly given by the formula included in Table 11. However, equation (4) can be used since  $r < R$ . Assuming that the length of the canal is one half of a circumference then

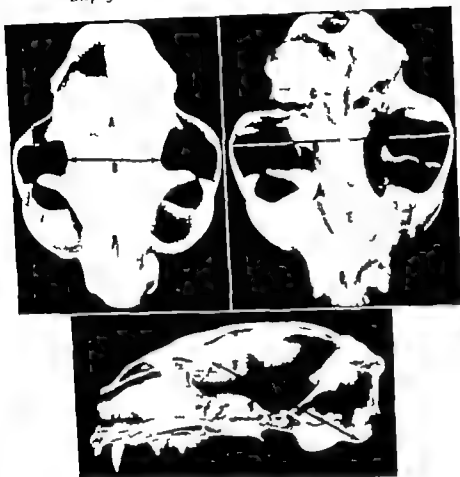


FIG. 1. Dorsal, ventral and medial views of the skull (male cat, 5.2 kg). Horizontal diameters whose values are reported in Table 1: A) bipuperal; B) bifrontal; C, lateral tympanic; D) barygomatic; E) foramen-mastoid; and F) foramen-frontal.

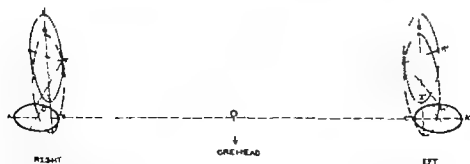


FIG. 2. Diagram of the semicircular canal showing the notation of the distances reported in Table 2. On the right side the solid line ABCD represent the horizontal canal, the broken line EFGH the anterior canal, and the dotted line IJK the posterior canal. On the left side, the corresponding canal are shown.

## METRIC CHARACTERISTICS OF CAT LABYRINTH

Two types of observations were made macroscopic and microscopic measurements

## A Macroscopic Measurements

## 1 Craniometry

A set of nineteen adult cats of both sexes, weighing between 16 and 4.5 kg, were taken at random for measuring the diameters shown in Fig 1. The purpose of these measurements was to find out whether the increase in size of the head due to age and sex may be associated with variations in the distances between semicircular canals. The measurements showed a large variation in the dimension of both bizygomatic and foramen incisors diameters while the dimension of the bifrontal inter tympanic bitemporal and foramen frontal diameters tended to be more constant (Table 1). Perhaps the size of the head as measured by these diameters or its weight or volume are more important for estimating the phylogenetic adaptation of the semicircular canal sensitivity and time constant of cupular return rather than changes in animal shape and body mass as postulated by Jones & Spells (1963)

## 2 Semicircular canals

The radius of curvature  $R$  and distances between canals, both unilateral and bilateral are important measurements for the theory of the cupula endolymph mechanism. From these measurements other distances or relationship between semicircular canals can be calculated.

The distances were determined in seventeen of the skulls mentioned in the previous section. In thirteen of the skulls, the periotic capsule was exposed under a dissecting microscope. The osseous semicircular canals of each skull were carefully open in their total length that is, from ampulla to their opening in the vestibule. Then the skull was rigidly mounted on a Johnson's stereotaxic instrument. The distance between two points on either side and the distance from one point on the right side to the cor

TABLE 1 Diameters of the skull

Diameter	Skulls (n)	M (mm)
Bifrontal	19	32.8 ± 3
Inter tympanic	10	37.2 ± 2.0
Bitemporal	10	33.0 ± 3.0
Foramen-frontal	14	50.0 ± 3.5
Bizygomatic	19	61.1 ± 6.6
Foramen incisors	18	67.7 ± 7.3

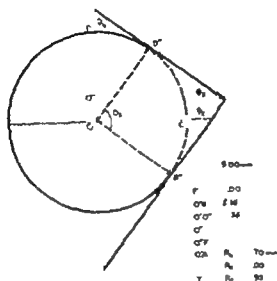


Fig. 3 Diagram illustrating the projection of the semicircular canal on the horizontal plane. The lines of glass through a region in the test.  $R_h$ ,  $R_p$  are the radii of curvature for the horizontal, anterior vertical and posterior vertical canal respectively. The angle subtended the arc of the horizontal canal with the utricle. The values given in the insert were taken from data of Table 2 but the values were rounded off to the nearest integer.

joined forming the common crus (Fig. 4). The distances from various points represented in this figure to the mid-sagittal plane SP can be calculated from Table 2.

### B. Microscopic Measurements

Histological sections of normal temporal bones were used for measuring the osseous and membranous diameters of each semicircular canal and common crus, and also for measuring cross-section areas of various vestibular structures. From this data the radius and volume of the structures were then calculated.

For measuring the membranous and osseous diameters, serial sections of temporal bones were used. Each section was projected onto a white surface at a magnification of 71:1 and diameters measured with a calibrated ruler. The distortion produced by the amplification was so small that no correction factor was used.

The measurements of areas were done in the temporal bones of two cats (A-1371 and B-252) by projecting (71:1) upon a cardboard the vestibular area of each section. The outlines of different structures were carefully traced and their area measured with a planimeter. In cat A-1371 one every five sections and in cat B-252, on every ten sections were drawn through the temporal bones of both sides. These areas were used for calculating

TABLE 2 Averages  $\bar{x}$  in mm of bilateral and unilateral distances between canals

See Fig 2 for identification of segments represented by capital letters. n=number of observations.

*Horizontal canal (HC)*

	CC	AA	AC	BD	AC'	B'D
n	65	60	55	55	60	60
$\bar{x}$	$25.0 \pm 0.8$	$31.3 \pm 0.9$	$3.2 \pm 0.3$	$3.5 \pm 0.3$	$3.4 \pm 0.4$	$3.5 \pm 0.3$

*Anterior vertical canal (AVC)*

	FF'	HH	HH'	EG	F'H'	EG
n	70	65	60	60	60	60
$\bar{x}$	$23.2 \pm 0.9$	$28.1 \pm 1.0$	$3.6 \pm 0.3$	$3.5 \pm 0.4$	$3.6 \pm 0.4$	$3.4 \pm 0.3$

*Posterior vertical canal (PVC)*

	AK	PK	IJ	F'A	I'J
n	70	70	65	0	60
$\bar{x}$	$28.0 \pm 1.0$	$3.1 \pm 0.3$	$3.2 \pm 0.3$	$3.3 \pm 0.3$	$3.0 \pm 0.2$

*Between AVC and PVC*

	HK	HK'
n	65	65
$\bar{x}$	$5.4 \pm 0.4$	$5.4 \pm 0.4$

responding point on the left as shown in Fig 2 were measured using a sharp needle mounted on the electrode holder of the stereotaxic device. Each distance was measured five times within the accuracy of the instrument that is, 0.1 mm. The numerical data are given in Table 2. In four additional skulls the temporal bones were filed down on either horizontal or vertical plane exposing some of the points shown in Fig 2. The direct measurements confirmed those obtained by dissection of the semicircular canals.

The data of Table 2 were used for constructing a geometrical figure which represented the projection of the canals on the horizontal plane. As shown in Fig 3 the horizontal canal appeared as a circle while the projection of the vertical canals formed a right angle tangential to the circle. For convenience the right angle was completed as a right triangle. The values of various segments are given in the table inserted in Fig 3. The values of the angles shown in the figure are the following:

$$\varphi_1 = \varphi_2 = 38.2 \quad \varphi_3 = \varphi_4 = 33.09 \quad \varphi_5 = 90$$

The point F in the figure represented the projection on the horizontal plane of the point where anterior vertical and posterior vertical canals

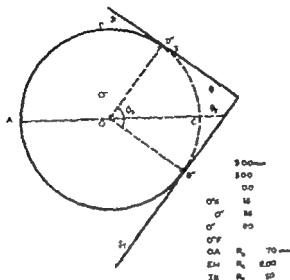


FIG. 2. Diagram illustrating the projection of the semicircular canal on the horizontal plane. The lines of sight through  $\phi$  are given. The  $R_h$ ,  $R_a$ ,  $R_p$  are the radii of curvature for the horizontal, anterior vertical and posterior vertical canal respectively. The angle  $\phi$  subtends the arc of the horizontal canal with the vertical. The angles given in the list were taken from column of Table 2 but the values were rounded off to the nearest integer.

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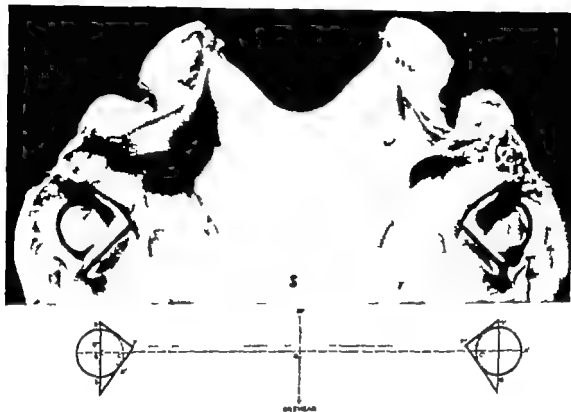


FIG. 4. Photograph of exposed semicircular canal seen from above. The lower diagram illustrates the projection of the canal on the horizontal plane. The value of the projection segment and angles can be found in Fig. 3 and Table 2. The distances from the distal point to the mid sagittal plane (SP) can be calculated from Table 2. Direct measurement can be made on the figure by using the scale  $s = 10$  mm.

the volume of both endolymph and perilymph and the volume of the membranous tissue forming the maculae and ampullae. The calculations were done by means of the trapezoidal rule

$$V = h \left[ \frac{1}{2} (y_0 + y_n) + \sum_{i=1}^{n-1} y_i \right] \quad (1)$$

where  $y_0, y_1, \dots, y_{n-1}, y_n$  are the values of areas measured and  $h$  is the thickness of each section times the number of sections between two consecutive measurements. The thickness of each section was  $20 \pm 2 \cdot 10^{-2}$  cm. Since the measurements were made in one every five sections in cat A 1371 and one every ten sections in cat B 212 the values of  $h$  were  $10^{-2}$  cm and  $2 \cdot 10^{-2}$  cm respectively. We must point out however that the intervals between two successive histological sections used for this purpose were sometime irregularly spaced. This irregularity however does not introduce an important error in the final result.

### 1. Semicircular canals

In most sections the contour of either membranous or osseous canal appeared as an ellipse. This is due to the direction of the plane of section

TABLE 3 Diameter  $d$  in mm of osseous and membranous semicircular canals

Number of observations

		Horizontal	Anterior	Posterior
Osseous	$d$	$0.29 \pm 0.01$	$0.29 \pm 0.01$	$0.27 \pm 0.02$
	$n$	9	7	6
Membranous	$d$	$0.23 \pm 0.01$	$0.23 \pm 0.02$	$0.21 \pm 0.01$
	$n$	9	6	5

relative to the plane of the canal. Thus, the diameter of both membranous and osseous canal was defined as the smallest value of all measurements made in the right and left temporal bones. The averages of all diameters and their radii were calculated and the results summarized in Table 3. The data showed that in the cat the largest difference between radius of membranous canal and that of osseous canal was about  $40 \mu$  (see Fig. 2).

The length of each semicircular canal is important for theoretical considerations. Some investigators consider the canal as a complete ring others estimate it as one half of a circumference while in fact it is neither one nor the other; each canal is an incomplete ring attached to a relatively large cavity, the utricle. Furthermore, the ampullary end of each canal is an other relatively large cavity intercalated between the canal proper and utricle. The ampulla is widely open into the utricle as shown in Fig. 3. Finally, the critical canals are open into an other relatively large cavity, the common crus, intercalated between their non-ampullary end and the utricle. Consequently the length of any semicircular canal is a matter of definition. If we consider it as a complete ring, then the length  $L = 2\pi R$  ( $R$  is the radius of curvature shown in table of Fig. 3). This calculated length was in agreement with that measured directly by passing a fine silver wire through the ring formed by the canal and vestibule. The length of the wire was then measured on a ruler. The data collected in thirteen pairs of bones (26 direct measurements for each canal) showed that the length of the ring for the horizontal, anterior and posterior canal was 10.6 mm, 11.3 mm and 10.0 mm respectively.

If we assume that each canal is an incomplete ring, then its length  $L$  is given by  $L = \varphi R$ . The values of  $\varphi$  were computed after measuring in each canal the chord  $L$  formed by the ends of the incomplete ring. The angle  $\varphi$  subtended by this chord was calculated so that  $\varphi = 2\pi - \varphi$ . The resulting data are given in Table 4. It is perhaps important to point out that in these data, each canal is considered as an incomplete ring of uniform diameter extending from one utricular end to the other.

A third definition is to consider as canal or canal proper that part of the ring excluding the utricle, ampulla and common crus. Table 5 shows



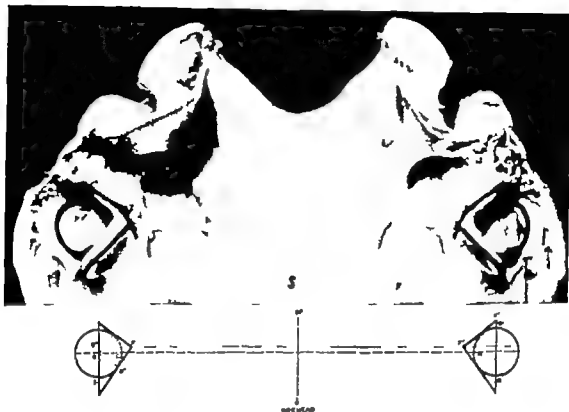


FIG. 4. Photograph of exposed semicircular canal in a cat seen from above. The lower diagram illustrates the projection of the canal on the horizontal plane. The values of various segments and angles can be found in Fig. 3 and Table 2. The distances from indicated point to the mid-sagittal plane (SP) can be calculated from Table 2. Direct measurement can be made on the figure by using the scale = 10 mm.

the volume of both endolymph and perilymph and the volume of the membranous tissue forming the maculae and ampullae. The calculations were done by means of the trapezoidal rule,

$$V = h \left[ \frac{1}{2} (y_0 + y_n) + \sum_{i=1}^{n-1} y_i \right] \quad (15)$$

where  $y_0, y_1, \dots, y_{n-1}, y_n$  are the values of areas measured and  $h$  is the thickness of each section times the number of sections between two consecutive measurements. The thickness of each section was  $20 \mu = 2 \times 10^{-2}$  cm. Since the measurements were made in one every five sections in cat A 1371 and one every ten sections in cat B 252, the values of  $h$  were 10 cm and  $2 \times 10^{-2}$  cm respectively. We must point out however that the intervals between two successive histological sections used for this purpose were sometimes irregularly spaced. This irregularity however does not introduce an important error in the final result.

### 1. Semicircular canals

In most sections the contour of either membranous or osseous canal appeared as an ellipse. This is due to the direction of the plane of section

TABLE 4 *Biometric data of horizontal anterior and posterior semicircular canals*

$L$  = Chord between ampulla and vestibular end of canal;  $R$  = radius of curvature;  $\phi$  = angle subtended by  $L$ ;  $\phi = 2\pi - \phi$ ;  $L$  = length of canal calculated from equation  $L = \phi R$ ;  $L$ ,  $L$  and  $R$  in mm;  $\phi$  and  $\phi$  in radians.

	Horizontal	Anterior	Posterior
$L$	2.20	2.83	2.17
$R$	1.70	2.00	1.50
$\phi$	.2	.434	.41
$\phi$	3.12	2.834	7.11
$L$	8.0	9.7	8.0

was  $1.83 \pm 0.05$  mm. The calculated volume of endolymph and perilymph contained in the common crus was  $22 \times 10^{-6}$  cm<sup>3</sup> and  $267 \times 10^{-6}$  cm<sup>3</sup> respectively. A comparison with the volume of the semicircular canal shows that the volume of endolymph in the common crus ( $22 \times 10^{-6}$  cm<sup>3</sup>) is as large as the total volume of the three canals per ear ( $873 \times 10^{-6}$  cm<sup>3</sup>). Perhaps, the geometry and expansion represented by the common crus may have some effect upon the motion of endolymph in the vertical canals.

### 3. Ampulla

We consider that the ampulla of the semicircular canals can be represented by a semi sphere of volume  $V = (2/3) \pi r^3$ . From the volume calculated by the trapezoidal rule the cross-section radius  $r$  was calculated (Table 5).

A distance of some importance for understanding the mechanics of the cupular motion is the radius of cupula deflection. This "radius of cupular deflection" will be the distance from the axis of rotation to the membranous wall of the ampulla. We assumed that the axis of rotation passes along the long axis of the crista is located about its foot as shown in Fig. 8. For

TABLE 5 *Length in mm of the canalicular system*

	Utriculus	Ampulla	Canal proper	Common crus	Total
Horizontal	2.1	0.73	7.87		10.6
Anterior	2.2	0.87	6.60	$1.83 \pm 0.05$	11.3
Posterior	2.1	0.81	5.12	$1.83 \pm 0.05$	10.0

Direct measurement on histological sections.

D is from direct measurements on histological sections.

Total length is length of utriculus, ampulla and common crus.

N is of 30 samples.

Mean of 26 direct measurements.

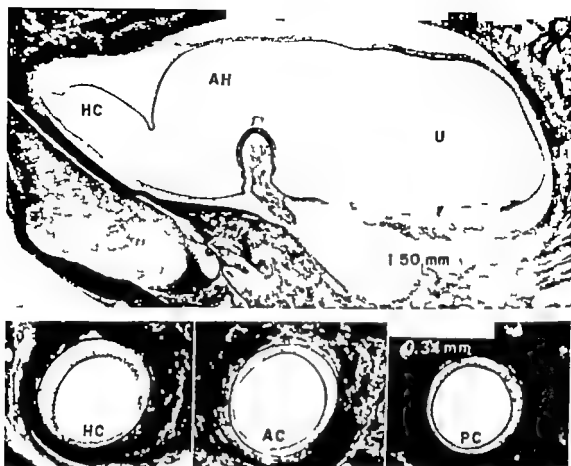


FIG. 5. Upper photomicrograph shows the relation between utricle (U) and ampulla (AH) of the horizontal canal (HC).

Lower photomicrograph shows a cross-section of the horizontal canal (HC), anterior vertical canal (AC) and posterior vertical canal (PC). Note that the magnification for these photomicrographs is different from that of the upper.

the length of each structure as collected from data already given or presented later on.

The volume of either osseous or membranous canal will depend on our definition. The volume of the canal proper was defined as  $V = \pi r^2 L$  where  $r$  is cross section radius and  $L$  length of canal proper. The calculated volume for each canal proper is:

Horizontal	$206 \times 10^{-6} \text{ cm}^3$
Anterior	$345 \times 10^{-6} \text{ cm}^3$
Posterior	$232 \times 10^{-6} \text{ cm}^3$

## 2. Common crus

The shape of both membranous and osseous walls of the common crus are elliptical. The measurements carried out in serial sections of two temporal bones are presented in Table 6. The length of the common crus was determined from 20 direct measurements on the skull. The value obtained

TABLE 6 Average diameter  $\bar{x}$  in mm of the short and long axes of the common crura

—X number of temporal bones.

Osteous				Membranous			
Right		Left		Right		Left	
Short	Long	Short	Long	Short	Long	Short	Long
10	6	10	6	10	6	10	6
$0.70 \pm 0.07$	$1.21 \pm 0.02$	$0.69 \pm 0.05$	$1.22 \pm 0.02$	$0.56 \pm 0.01$	$0.99 \pm 0.07$	$0.54 \pm 0.01$	$0.95 \pm 0.07$

	Average	
	Short	Long
Osteous	0.69	1.23
Membranous	0.55	0.96

## 5 Utriculus

The shape of the utriculus appeared as an elongated body with an elliptical shape in cross-section. The long axis was determined in the serial sections of twelve cats. The number of sections containing the structure times their thickness yielded a length of 2.2 mm. The diameters of the ellipse which appeared in cross-section were measured directly in 16 ears. The averages were 0.835 mm and 1.20 mm for the short and long diameters respectively.

The volume of the utriculus was calculated from the ellipsoid formula ( $V = \frac{4}{3} \pi abc$ ) and from the trapezoidal rule (equation (15)) was  $110 \pm 10 \text{ } \mu\text{m}^3$  and  $1363 \cdot 10^{-6} \text{ cm}^3$  respectively. On the assumption that the utriculus was a sphere the radius  $r$  and the cross-section area were calculated (see Table D).

## 6 Volume of the Labyrinth

The volume of the vestibule including endolymph, perilymph and soft tissue of sacculus, utriculus and cristae were calculated by the trapezoidal

TABLE 7 Volume of vestibular sense organs in 10 mm

	Endolymph	Perilymph	Soft tissue	Total
Vestibule	1978	7685	140	11103
Canals	873	318		1191
Utriculus	1412	507	511	2430
Laminar crura	722	567		1289
Total	4215	9070	2281	16566

The volume of the canals is that of the three canal proper.



FIG. 6. Photomicrograph of a section passing about the plane of the horizontal canal (hc) utricle (u) radius of cupul deflection (rd) (0.048 mm).

accurate measurements of this distance it was necessary to process temporal bones so that the plane of section was parallel to the plane of the canal and therefore perpendicular to the long axis of the crista (Fig. 6). The measurements showed that the radius of cupular deflection for each canal were the following:

Horizontal	0.048 mm
Anterior	0.803 mm
Posterior	0.030 mm

#### 4. Sacculus

The volume of the sacculus as calculated by the trapezoidal rule was  $1.616 \times 10^{-6} \text{ cm}^3$ . On the assumption that the sacculus may be represented as a sphere the radius,  $r$ , and the cross section area were calculated (see Table 9).

data of the vestibular sense organs in our series of animals and in those reported by others, showed a remarkable constancy of their dimensions. For instance our measurements regarding the value of  $r$  and  $R$  are in agreement with those reported by Igara hi (1966). The length of the semicircular canals is a measurement which seems to be at variance among authors. For instance the values given by Wulf (1961) also given by Gray (1963) and Camis (1966) for the horizontal anterior and posterior semicircular canals of the cat were 1.5 mm, 4.5 mm and 4.5 mm respectively. These values are close to those given by our definition of canal proper but are quite different from the values given for the canal as an incomplete or complete ring. These discrepancies between investigators is probably due to differences in the definition of what is measured as a semicircular canal.

The length  $l$  of the semicircular canal is included in the calculation of  $\Pi$  as shown in equation (1). Thus, the time constant of the cupula return as defined by equation (12) will show some variation according to what is meant by length of the semicircular canal. The variation, however, seems to be insignificant. If we consider a semicircular canal the incomplete ring by excluding the utricle, then the time constant  $t$  for each canal is the following:

Horizontal canal

$$\begin{aligned} L_1 &= \frac{3\pi}{2} R \\ \Pi &= 12\pi \eta R^3 \\ \Delta &= \pi \mu^2 R_1 \\ t = \frac{\Pi}{\Delta} &= \frac{12\pi \eta R^3}{\mu^2 R_1} = \frac{12\pi \eta}{\mu^2} \frac{R^2}{R_1} \times 10^3 \text{ (sec).} \end{aligned}$$

Anterior vertical canal

$$\begin{aligned} L_2 &= 1.55\pi R_p \\ \Pi &= 12.4\pi \eta R_p^3 \\ \Delta &= \pi \mu^2 R_{v2} \\ t = \frac{\Pi}{\Delta} &= \frac{12.4\pi \eta R_p^3}{\mu^2 R_{v2}} = \frac{12.4\pi \eta}{\mu^2} \frac{R_p^3}{R_{v2}} \times 10^3 \text{ (sec)} \end{aligned}$$

Posterior vertical canal

$$\begin{aligned} L_3 &= \frac{\pi}{4} R_2 \\ \Pi &= 14\pi \eta R_p^3 \\ \Delta &= \pi^2 \mu^2 R_{v2} \\ t = \frac{\Pi}{\Delta} &= \frac{14\pi \eta R_p^3}{\mu^2 R_{v2}} = \frac{14\pi \eta}{\mu^2} \frac{R_p^3}{R_{v2}} \times 10^3 \text{ (sec)} \end{aligned}$$

TABLE 8 *Extrinsic characteristics of the semicircular canals*

	HC	AC	PC
Distance in mm from sagittal plane to:			
Center of canal	14.1	12.9	12.9
Outermost point of canal	15.7	14.1	14.1
Innermost point of canal	12.4	11.7	11.7
Angle between canal plane and:			
Horizontal plane	0	90	90
Sagittal plane	90	36.52	53.08
Frontal plane	90	53.08	36.52

rule in four temporal bones. The averages of this calculation are presented in Table 7. The soft tissue shown in the last column of the table represents the volume of tissue forming the macula of sacculus and utriculus and that of the three cristae ampullares. The membranous walls were not calculated because their value is insignificant as compared to that of the sensory epithelium.

### C. Summary of Biophysical Data

In Table 8 some extrinsic metric characteristics of the semicircular canals are summarized. The most important intrinsic measurements are presented in Table 9.

TABLE 9 *Intrinsic metric characteristics of cat labyrinth*

$r$ —Radius;  $F$ —area;  $R$ —radius of curvature of canal;  $L$ —length of canal;  $A$ —area of circle.

	HC canal			AVC canal			PVC canal			Sacculus (Utriculus)	
	Osseous	Membr.	Ampulla	Osseous	Membr.	Ampulla	Osseous	Membr.	Ampulla	Sacculus	Utriculus
$r$ (cm)	0.014	0.011	0.064	0.014	0.013	0.038	0.013	0.012	0.060	0.053	0.070
$R$ (cm)	0.17	0.17		0.20	0.20		0.15	0.1			
$L$ (cm)	1.06	1.06		1.13	1.13		1.06	1.06			
Circle area ( $\pi R^2$ ) cm <sup>2</sup>	0.09	0.09		0.13	0.13		0.07	0.0			
Cross-section area ( $\pi r^2$ ) $10^{-4}$ cm <sup>2</sup>	6.1	3.8	128.	6.3	5.3	106.8	3	4.4	148.6	88.0	151.0
Volume ( $10^{-4}$ cm <sup>3</sup> )	493	403	546	360	533	400	437	373	604	610	1,263

### DISCUSSION

The craniometric data revealed a considerable variation in size of the skull of the so-called young adult cat. On the other hand, the biometric

TABLE 10 Endolymph moment of inertia

$\rho = 1.000$  (gm/cm<sup>3</sup>);  $D$  = distance from center of semicircular canal to midline of plane;  $L$  = length of the canal circle

Canal	$r$ (cm)	$R$ (cm)	$L$ (cm)	$D$ (cm)	$m = \pi \rho L$ (gm)	$\Theta = m(R^2/2)$ (gm cm <sup>2</sup> )	$\Theta' = \Theta + mD^2$ (gm cm <sup>2</sup> )
HC	0.011	0.17	1.06	1.41	4.06 $10^{-4}$	0.12 $10^{-4}$	8.20 $10^{-4}$
AVC	0.013	0.20	1.13	1.29	5.60 $10^{-4}$	0.22 $10^{-4}$	9.70 $10^{-4}$
PVC	0.013	0.18	1.00	1.29	4.40 $10^{-4}$	0.10 $10^{-4}$	7.33 $10^{-4}$

If the values of  $\Pi$ ,  $\Theta$  and  $\Pi/\Theta$  have been calculated with the assumption that the viscosity of endolymph is like that of water. The corresponding values for the pigeon as given by Money *et al.* (1966) are incorporated into this table for comparison. After considering the anatomical differences between cat and pigeon and that the density and viscosity of the cat endolymph is not known yet, the comparison shows consistency of results between the two species. From these observations, we may conclude that the fundamental differential equation for the canal-cupula endolymph system must be separately applied to each canal in any analytical mechanical study of the labyrinth.

Our measurements confirmed the postulate of Jones & Spells (1963) as stated in equation (1) for mammals. The calculation of  $r$  (with  $n = 0.1818$  and  $k = 0.0430$ ) for our cats with lowest weight (17 kg) and highest weight (3.0 kg) was 0.011 cm and 0.012 cm respectively. This is in agreement with the values of  $r$  as calculated from measurements presented in Table 2. Similarly the calculated value of  $R$  from equation (1) (with  $n = 0.1187$  and  $k = 2.2460$ ) gave 0.18 cm and 0.21 cm for the lightest and heaviest cat respectively. This again is in agreement with our measurements presented in Fig. 3. Although our results confirmed the observations of Jones & Spell (1963) still the question remains whether their postulate will be consistent with accurate measurements of each canal in a large variety of species.

TABLE 11 Values of  $\Pi$ ,  $\Theta$  and  $\Pi/\Theta$ 

$\Pi$  is  $\eta \pi^2 R^4 / 4$ ;  $\eta$  is  $1.000 \times 10^{-2}$  (gm/sec cm)

Canal	Cat			Pigeon <sup>a</sup>		
	$\Pi$ (dynes cm/sec)	$\Theta$ (gm cm <sup>2</sup> )	$\Pi/\Theta$ (sec <sup>-2</sup> )	$\Pi$	$\Theta$	$\Pi/\Theta$
HC	7.89 $10^{-8}$	0.12 $10^{-4}$	857	7.8 $10^{-8}$	0.21 $10^{-4}$	360
AVC	12.63 $10^{-8}$	0.22 $10^{-4}$	573	22.0 $10^{-8}$	1.5 $10^{-4}$	190
PVC	3.36 $10^{-8}$	0.10 $10^{-4}$	336			

Data from Money *et al.* (1966)



If the canals are arranged in the decreasing order of  $R$  then the relationship  $t_2, t_1, t_3$  can be calculated. The results are the following

$$t_2/t_1 = 0.99 \quad t_1/t_3 = 1.31 \quad t_2/t_3 = 1.51$$

Therefore if we take the time constant of the semicircular canal with smallest  $R$  (posterior vertical canal) as unity then we can write the cupula recovery function (equation (11)) for each canal as follows

$$\begin{aligned} \text{HC} \quad t_1 &= 1.51 t_3 \text{ (sec)} & \beta_1 &= \beta_0 e^{-t/t_1} \\ \text{AVC} \quad t_2 &= 1.51 t_3 \text{ (sec)} & \beta_2 &= \beta_0 e^{-t/t_2} \\ \text{PVC} \quad t_3 &= 1.0 \text{ (sec)} & \beta_3 &= \beta_0 e^{-t/t_3} \end{aligned}$$

We would like to point out that these values for the cupula recovery function represent a theoretical approximation based on our measurements of both radii  $r$  and  $R$ .

The graphs of these functions are shown in Fig. 7. The derivative of equation (11) for  $t=0$  is

$$\frac{d\beta}{dt} = -\frac{\beta_0}{t} \quad (16)$$

This shows that the tangent at the origin intersects the time axis at the value corresponding to the time constant  $t$ .

In Table 10 the moment of inertia of the endolymph with respect to the canal center and to the mid sagittal plane has been calculated assuming that the density of the endolymph is equal to that of water. It is obvious that the absolute value of these moments of inertia cannot be determined accurately until the density of endolymph in the cat is measured. In Table

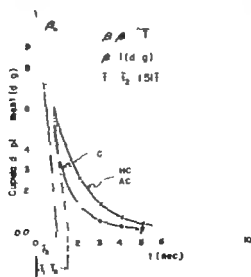


FIG. 7. Function of the cupular return for each canal: HC, horizontal canal; AVC, anterior vertical canal; PVC, posterior canal.

## NYSTAGMUS RATE AS AN INDEX OF CALORIC TEST RESPONSE

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Using sample of 20 otologically normal adults, the number of nystagmus beats in the period 60 to 90 second after the onset of irrigation was found to be valid measure of caloric test response. This value shows a Gaussian distribution, as does the two-ear difference. In this value after logarithmic transformation utilising a 10% probability level, less than 33 beats in this period would be abnormal, & would a difference of more than 20 beats between the two ears.

### INTRODUCTION

Some otologists use the number of beats over a given period of time as an index of response to vestibular stimulation. The validity of this measure has been questioned.

In a recent report (Hinchcliffe 1967a) evidence was presented to indicate that, of a number of measures of caloric test response only the maximum velocity of the slow phase of nystagmus induced by an ampullo-petal stimulus (specifically the hot caloric irrigation in the conventional supine position) was a valid measure of vestibular function. Unfortunately in that analysis a measure of nystagmus frequency (beat rate) was not included.

It is the purpose of this paper to assess the validity of nystagmus frequency as an index of vestibular responses to thermal stimulation and to furnish some data on the normal range of measurements. Since the maximum velocity of the slow phase of nystagmus has already been shown to be a valid measure of caloric response the nystagmus frequency may be cross-validated by determining the correlation existing between these two measures.

### PROCEDURE

The caloric test was administered to 20 otologically normal adults with no history of vertigo or other aural symptoms and the induced nystagmus was recorded electro-oculographically. The method of testing was as described in a recent paper (Hinchcliffe 1967b) with water at 44°C only being used and the subject lying in the conventional supine position. Six

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## ZUSAMMENFASSUNG

Eine Untersuchung über die biophysikalischen Dimensionen des Labyrinths der Katze wurde vorgenommen. In jedem Bogengang wurden der Durchmesser der häutigen und der knöchernen Bogengänge und die Radien der Krümmung gemessen. Die Länge und der Umfang der Bogengänge wurden errechnet. Auch der Umfang des Sacculus, Utriculus, der Endolymph und Perilymph wurde nach dem Messen ihrer Flächen in histologischen Reihenschnitten errechnet. Die Abstände zwischen den Bogengängen wurden auch gemessen und die Winkel zwischen ihnen bestimmt. Diese Angaben wurden zur Errechnung der Konstante der fundamentalen Differentialgleichung des Cupula Endolymph Systems benötigt.

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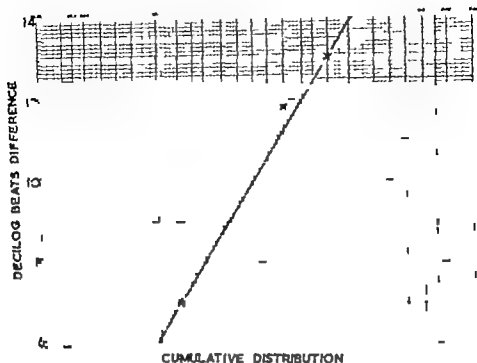


FIG. 2. Cumulative distribution of the difference between the two ears for the number of nystagmus beats in the 30-second period. Twenty of logically normal adults.

on this type of graph paper.) The frequency distributions for the difference in the number of beats between the two ears, although unimodal, was skewed to the left. However, plotting this data on arithmetical probability paper after a logarithmic transformation indicated that this transformed distribution was Gaussian also (Fig. 2). The principal values for the distribution of these measures are shown in Table 1.

Table 2 shows the correlations that existed between the maximum velocity of the slow phase and the total number of beats in the period 1 min to 1 min 30 sec following onset of irrigation of the ear. The table indicates an overall correlation coefficient of about 0.63, which is significant at the  $p < 0.01$  level.

TABLE 1. Principal values for the distribution of two measures of nystagmus beat rate on 20 otologically normal adults.

Measure	Average	10%ile	90%ile
Total beats from 00 to 90 sec	58	33	80
Two-ear difference in this total	10	5	20

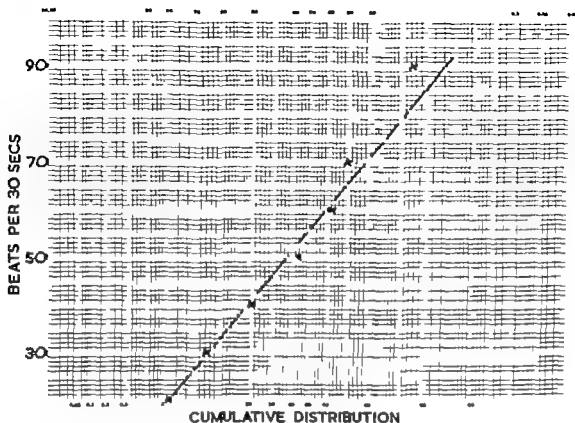


FIG. 1 Cumulative distribution of the number of nystagmus beats in the period 60 to 90 seconds after the onset of irrigation of an ear with water at 44°C. Data from a sample of 20 otologically normal adults (40 ears)

teen of these subjects were available for retesting and a second caloric test was given to these individuals. For this group also a correlation matrix was obtained to determine the correlations existing between the maximum velocity of the slow phase of the induced nystagmus and the number of nystagmus beats in the period 1 min to 1 min 30 sec following the start of irrigation of the ears. Correlations were determined for both the right and the left ears separately and for the two occasions of testing.

In order to determine the range of values, the frequency distribution of the number of nystagmus beats that occurred in the period 1 min to 1 min 30 sec for each of the 40 ears of the initial samples was examined. The frequency distribution of the difference between the two ears in the number of beats over this period was also examined.

## RESULTS

The total number of beats in the period 1 min to 1 min 30 sec was found to give a unimodal frequency distribution and plotting the data on arithmetical probability paper (Fig. 1) indicated that this was a Gaussian distribution. (A Gaussian distribution gives a straight line when plotted

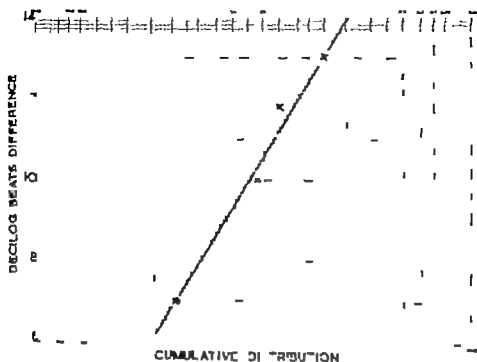


FIG. 2. Cumulative distribution of the difference between the two ears for the number of nystagmus beats in the 30-second period. Twenty otologically normal adults.

on this type of graph paper.) The frequency distributions for the difference in the number of beats between the two ears, although unimodal, was skewed to the left. However plotting this data on arithmetical probability paper after a logarithmic transformation indicated that this transformed distribution was Gaussian also (Fig. 2). The principal values for the distribution of these measures are shown in Table 1.

Table 2 shows the correlations that existed between the maximum velocity of the slow phase and the total number of beats in the period 1 min to 1 min 30 sec following onset of irrigation of the ear. The table indicates an overall correlation coefficient of about 0.83, which is significant at the  $p < 0.01$  level.

TABLE 1. Principal values for the distribution of two measures of nystagmus beat rate on 20 otologically normal adults.

Measure	Average	10th	90th
Total beats from 60 to 90 sec	86	33	90
Two-ear difference in this total	10	5	20

TABLE 2 *Correlation coefficients calculated for the number of nystagmus beats in the period 60 to 90 seconds after start of ear irrigation and the maximum velocity of the slow phase of the induced nystagmus*

Coefficients are given for right and left ears and test and re-test separately. Sample of 16 otological normal adults.

Ear	Test	
	First	Second
Right	0.71	0.64
Left	0.60	0.62

## DISCUSSION

The results (Table 2) indicate that the total number of nystagmus beats counted over the period of 1 min to 1 min 30 sec subsequent to the start of irrigating the ear with water at 44 C with the subject in the supine position is a valid measure of vestibular response, inasmuch as this measure is highly significantly correlated with the maximum velocity of the slow phase of the induced nystagmus.

Until the caloric test can be administered to a random sample of the general population the distributions given in Figs 1 and 2 provide provisional data for ascertaining the normality or otherwise of caloric test records. A composite group of both sexes and various ages was taken because as far as adults are concerned these two variables do not appear to be prominent factors in determining beat frequency.

It is to be noted that nystagmus frequency has an advantage over maximum velocity of the slow phase in the assessment of a caloric response inasmuch as the measurement is the more easily and rapidly determined.

## CONCLUSIONS

The number of nystagmus beats occurring in the period 1 min to 1 min 30 sec after irrigation of an ear with water at 44 C for 30 sec and recorded electro-oculographically is shown to be a valid measure of vestibular response.

Data obtained from normal subjects indicate that if the number of beats in this period and under these conditions is less than 33 or the difference in the number of beats in this period between the two ears is more than 20 then the response is probably abnormal.

## ZUSAMMENFASSUNG

Bei 20 Erwachsenen mit normalem Gehör wurde die Anzahl von Nystagmusschlägen während der Zeitspanne von 60–90 sec nach Beginn der Irrigation als ein gültiges Mass bei kalorischer Versuchsreaktion befunden. Dieser Gehalt

zeigt eine Gaußsche Verteilung, ebenso wie die 2-Ohr-Variationsbreite in diesem Gehalt nach ihrer logarithmischen Umbildung. Bei Anwendung eines 10 prozentigen Wahrscheinlichkeitsgrades würden weniger als 1% Pulschläge während dieser Zellspanne abnorm sein, ebenso wie ein Unterschied von mehr als 20 Pulschlägen zwischen den beiden Ohren.

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## ON THE MIDDLE EAR OF BIRDS

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The structural and functional peculiarities of the middle ear taken from various species of birds have been studied on 80 preparations. The results of a morphological and functional study of the avian middle ear have been compared to the anatomy and physiology of the human ear in its normal status as well as after tympanoplasty. An analogous model of the avian tympanic apparatus has been designed.

### INTRODUCTION

The study of the structure of the avian ear began a long time ago. The first publication dates back to the year 1600 (Casseri). One of the first investigations of the avian ear was made by a physician from Riga Wilpert who defended his thesis in 1804 on the theme "De differentia organi auditus animalium". Here he states the characteristic features of the structure of the avian ear saying: "Membrana tympani avium in superficie externa convexa. Aves unicum tantum ossiculum proffident." Thus Wilpert had already noted the main peculiarities of the tympanic structure in birds: a tympanic membrane that is external to the outside like a tent and the existence of a single ossicle, which afterwards was appropriately called a columella—meaning small column.

The following authors have similarly investigated the ear of birds: Breschet (1836), Huxley (1869), Parker (1869, 1879), Wurm (1874), Graff (1885), Hennicke (1889), Gaupp (1898), Suchkin (1899), Smith (1904), Denker (1907), Breuer (1908), Pohlman (1921), Yoshitsune (1924), Dombrowsky (1925, 1926), Jellinek (1926), Stellbogen (1930), Wassiljew (1933), Scheestakowa (1934, 1941), Stresemann (1934), Schemmizky (1935), Wever & Bray (1936), Ibusaki (1938), Brand & Kellogg (1939), Granit (1941), Guggenheim (1948), Portmann (1948, 1950), Punphrey (1948, 1960), Prosser, Bishop, Brown, John & Wolff (1950), Buddenbrock (1952), Freye (1952), Freye-Zumpfe (1952), Mazo (1952, 1954), Schwartzkopff (1952, 1955, 1956, 1960, 1962), Sturkie (1954), Shmalhausen (1954), Radonova (1958), Kirikae (1960, 1963), Vallancien (1963), and Lysuk & Makukha (1966). The most detailed descriptions of the avian ears have been made by Krause (1901)—40 species of birds—and Werner (1960).

This paper was read before the Meeting of the Estonian Otolaryngologic Society in Tartu (Dorpat) Dec. 20-21, 1963.

The publications of all the above mentioned authors are to be found in periodicals and monographies of different fields, such as the natural sciences, biology ecology zoology paleobiology ornithology and normal and comparative anatomy while in medical literature they are scarce. This makes it difficult for medical researchers to compile a bibliography on this subject. A failure to become acquainted with the available material leads frequently to contradictory and faulty concepts.

Nearly all the authors tend to characterize the middle ear of birds as a simplified one. Their attention is mainly directed to the fact that the birds possess only one auditory ossicle—the columella—which is situated directly between the tympanic membrane and the oval window.

The ear of birds has attracted attention in otology during the last 10 years in connection with the development of tympanoplasty, one basic principle of which is columellization, i.e. the concept of a seemingly simplified structure of the bird ear. Taking into consideration the fact that birds and mammals have developed simultaneously and independently while existing in similar acoustical conditions, a comparison of their ears is of extreme interest from the scientific point of view.

#### MATERIAL AND METHOD OF EXPLORATION

In order to study the avian ear the anatomical structure and the functional peculiarities of 80 preparations of several species have been explored: *Striges*—eagle-owls—*Bubones*—falcons—*Falcones*—crows—*Corvidae*—pigeons—*Columbae*—geese—*Anseres*—hens—*Gallus*. Anatomical exploration of the tympanic cavity were made by means of a binocular magnifying lens. Some characteristic features were fixed by taking macrophotographs.

##### *Anatomical Explorations of the Birds' Middle Ear*

It has been shown that birds have a single rod-like and relatively long auditory ossicle—columella, its proximal end extending perpendicularly to a plate called the ellipse (a shield) according to the terminology given by Krause (1901). The ellipse is oval in determining the size of the columella we were struck by its length. The comparative measurement of the length of the columella and the longitudinal diameter of the ellipse in various species of birds showed a constant coefficient, the column being steadily 3-4 times longer than the longitudinal diameter of the ellipse. That is one of the main differences between the columella of birds and the tapes of mammals. The height of the tapes in man is less than twice the length of the longitudinal diameter of its footplate.

The ellipse is fixed in the oval window by an annular ligament too. An examination under the microscope has shown this ligament to be broader at the anterior margin of the ellipse. That is why mainly the protrusion of the anterior edge are those which are determined when

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### INTRODUCTION

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probing the clipeolus. This serves as additional proof that the anatomical structure of the avian annular ligament is similar to that of humans.

Weber (1960) has pointed out that the columella in birds is lying at an acute angle to the plane of the tympanic ring (ca.  $30^\circ$ ) though he did not attach great importance to this fact. The columella approaches the tympanic membrane from behind. The distal end is attached to the tympanic membrane at the posterior margin. That is why the oval window is located behind and out of projection of the tympanic membrane. In this respect the ear of birds differs from that of mammals.

The extracolumella is connected by a synchondrosis to the distal end of the columella. In young bird the extracolumella is of a cartilaginous structure while in older ones it has become partly ossified. The extracolumella has been described by Huxley (1869) although its existence was ignored by otologists when they compared the middle ear of birds to that of man. In fact the extracolumella is an important additional structure in the tympanic apparatus of birds. The extracolumella consists of three processes—processus extra-, supra- and infracolumellaris. The biggest of these three is the exterior process continuing in the direction of the columella and like the handle of malleus in human is firmly attached to the dorsal radius of the tympanic membrane stretching from its posterior margin toward the centre.

In our opinion the essential peculiarities of the extracolumella which should be taken into consideration are the following. The "end-to-end" connection of the extracolumella to the columella leads to an elongation of the system of the auditory ossicles of birds. That such a condition should be established with tympanic membrane in bird protrudes contrary wise toward the external auditory meatus. As the tympanic membrane in birds is conically shaped, too an external inspection shows it to be tent-like.

The two remaining processes of the extracolumella pass upwards and downwards along the posterior margin of the tympanic membrane anchoring in it. The result is that in bird the auditory ossicles are not contacting in one point (as it occurs in mesotympanoplasties) but the tympanic membrane rests on the whole extracolumella, the shape of which resembles a tripod. This peculiarity is important enough to be taken into consideration, as such junction of the ossicles with the tympanic membrane accords with the ossicle complex—a membrane with a rod. The eardrum of man is constructed similarly having the function of a conical levator (Helmholtz, 1868).

#### No physiological Conclusions

When comparing the results received after the anatomical investigation of the middle ear of bird we may point out the following peculiarities as different from the structure of the human ear.



FIG. 1 Columella of the goose  $\times 13$

FIG. 2 The oval (1) and round (2) window viewed from the inner ear. The right band is broader at the anterior edge of the cilpeolus 20

FIG. 3 The extracolumella and columella of the owl



FIG. 4 The light tympanum of the goose viewed from below. The dorsal loci of the cilpeolus (1) and the incl. of the columella toward the tympanum (2)

FIG. 5 A side view of the tympanic membrane of the owl

1 The system of the auditory ossicles in birds is lengthened out. As an evolutionary necessity it follows that the oval window is dislocated backwards while the tympanic membrane protrudes outwards.

2 The common length of the auditory ossicles is greater than the longitudinal diameter of the clipeolus in 4 to 5 times.

3 The system of the auditory ossicles has an angle of inclination towards the tympanic ring.

*Similar features in the avian and human ears*

1 The ring-shaped attachment of the clipeolus and the footplate of the stapes are similar in construction enabling libration to occur mainly in the anterior part of the clipeolus and the footplate of the stapes.

2 The attachment of the auditory ossicle to the tympanic membrane by way of a conical lever (membrane-with-rod) is similarly shaped.

### *Functional Exploration of the Auditory Ossicles of Bird*

In the literature we come across the concept that a simplified structure of the avian ear combines with a simple mechanism of its elements in the tympanic cavity. It was believed that the columella transmits the acoustic vibrations of the tympanic membrane to the oval window pistonlike without transforming them in any way. Only Shmalhausen (1937) and Pumphrey (1960) expressed the opinion that the columella might serve as a specific transformer although they lacked experimental data to prove it.

In order to make a functional study of the auditory system of birds we have explored the mechanism of the displacement of the tympanic membrane and the columella under the influence of an alternating pressure of air in the external auditory meatus, considering that the pressure of sound is a variation of atmospheric pressure.

For this purpose fresh preparations of the birds' ears were taken, the tympanic cavities of which were opened from below to examine the columella and the interior surface of the tympanic membrane. A plastic tube was hermetically attached to the external auditory meatus and connected with a water manometer. An alternating positive and negative pressure was exerted on the tympanic membrane until a marked displacement by using a microscope took place. The displacement of the detailed parts in the tympanic cavity was studied by taking macrophotographs. In each experiment the tympanic cavity was photographed twice in sequence on the same slide with a double exposure during the extreme excursion of the membrane and auditory ossicles, which occurred as a result of the positive and negative pressure in the auditory meatus imitating an alternating sound pressure.

### *Results of Functional Explorations*

It appears that the tympanic membrane oscillates together with the columella and the distal end of the columella. As in human, the free



FIG 6 The interior view of the tympanic membrane with extracolumella and columella of the goose

FIG 7 External excursion of the columella (goose). The right side viewed from below. Oscillations of the columella in cross direction (by double position)



FIG 8. The exterior view of the tympanic membrane of the cock. Process of extracolumella is situated at the dorsal part of the tympanic membrane



FIG. 11. A schematic drawing of the tympanic system of the right avian ear from below (1) External auditory meatus; (2) tympanic cavity; (3) tympanic membrane (tortic part); (4) columella; (5) extracolumella; (6) lipculus (or lipculus); (7) round window; (8) rostrum; (9) membrana basilaris.

FIG. 12. Mechanical (kinetic) analogues model of the tympanic system of birds. (A) Position of silence; (B) position of extreme external displacement; (C) position of extreme internal displacement. (1) Tympanic membrane; (2) extracolumella; (3) columella; (4) lipculus.

shuttle back and forth the inert perilymph in the scalae. Thus it is clear why an elongation of the auditory ossicles has taken place during the phylogenesis of birds.

It is interesting to note that in the analogous vectorial model of the human tympanic system (Gandini, 1967) the auditory ossicles have the same specific weight in the correlation of the parameters of acoustic vibrations in matching the two systems.

### ZUSAMMENFASSUNG

Das Mittelohr der Vögel ist vom Standpunkt des anatomischen Aufbaus wie auch des Funktionsmechanismus eigenartig, und seine Anatomie und Physiologie unterscheidet sich vom menschlichen Ohr. Wenn die Koeffizienten der Transformationswirksamkeit der akustischen Vibrationen betrifft, so bleibt das Vogelohr dem menschlichen Ohr nicht nach. Daraus folgt, dass die Annahme von dem vereinfachten Aufbau und der Funktion des Vogelohres unbegründet ist. Dieser Annahme lag der sogenannte „columella effect“ zugrunde bei Rekonstruktionschirurgie des Mittelohrs zur Erklärung der morphologischen Analogismen nach solchen Operationen und zur Rechtfertigung einiger tympanoplastischen Verfahren die nicht experimentell bestätigt worden waren. Doch nach Operationen denen der „columella effect“ zugrunde gelegt wurde, ist klar, dass die erwähnten Merkmale des Aufbaus und der Funktion des Mittelohrs der Vögel in den neotympanalen Systemen beim Menschen vorhanden.



(anterior) part of the tympanic membrane receives the greatest displacement. Because of the sloping position of the columella towards the tympanic membrane its vibrations are transmitted by the column not longitudinally but in a transversal side excursion which occurs across the position of silence.

Therefore it is quite natural that the clipeolus does not oscillate symmetrically and pistonwise hence the anterior edge is mainly displaced. Thus the vibrations of the clipeolus in birds, figuratively expressed remind us of the movements of a musician's foot tapping as it rests on the heel. According to the investigations by Buck (1870) Wrightson & Keith (1918) Fumagalli (1949) and Wanderer (1953) similar asymmetric vibrations also occur in the footplate of the human stapes as a result of the function of the malleus and incus which act as levers.

### *Functional Conclusions*

A comparison of the physiological peculiarities of the middle ears in birds and humans makes it possible to remark on their differences and similarities. The main difference is in the character of the vibrations of the columella in birds which differs from the vibrations of the stapes after mesotympanoplasty when the so-called columella effect is produced.

A similarity between the mechanism of the middle ear of birds and humans can be detected when a comparison is made of the function of the tympanic membrane and by observing the specific displacements of the columella and the stapes, i.e. their side vibrations with "pedalling" of the clipeolus and the footplate of stapes.

### *An Analogous Model of the Avian Tympanic System*

Based on experimental observations of the function of the elements in the tympanic cavity and considering the anatomical peculiarities of the structure of the birds' ear we have designed an analogous model of the middle ear of birds. In this model the position of silence (A) and the extreme displacements of the tympanic membrane and the auditory ossicles during vibrations (B, C) have been presented.

It appears that on the whole the auditory ossicles work as a lever with two arms. The long arm is the column and the external process of the extracolumella. The short arm is represented by the longitudinal diameter of the clipeolus. Hypomochlion corresponds to the posterior edge of the clipeolus.

As in the ear of bird the long arm of the lever is 4-5 times longer than the short one and the amplitude of vibrations of the extracolumella is decreased by as many times compared to the vibrations of the anterior margin of the clipeolus. The pressure of sound increases accordingly to overcome the acoustic impedance of the air-liquid boundary in order to

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## DIE MIKROPRÄPARATION DER COCHLEA

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Ge aus Beschreibung der Mikropräparationstechnik der Cochlea. Sie ermöglicht eine schnelle und rasche Darstellung des Cortischen Organes, des Ligamentum spirale mit Stria vascularis sowie des Ganglion spirale und deren Veränderungen, wobei ein Cytocochleogramm die Auswertung der morphologischen Befunde statistisch sichert. Daneben lassen sich mit dieser Technik bei Gefrierpräparationen kleinste Peri- und Endolymphportionen gewinnen. Die Mikropräparation stellt so eine wichtige Methode zur Untersuchung der Cochlea dar.

Morphologische und biochemische Untersuchungen an den Strukturen der Cochlea — sei es, um Auskunft über physiologische oder über pathologische Vorgänge zu erhalten — haben letztlich das Ziel, Relationen aufzuzeigen, die sich später einmal für die Klinik, für die Behandlung unserer Patienten verwerten lassen. Dabei erfordert die Mannigfaltigkeit der Strukturen, die zahlreichen zu untersuchenden metabolischen Vorgänge eine Vielzahl verschiedener Methoden. Von diesen bevorzugen wir seit langem zur Darstellung der häutigen Cochlea die Mikropräparationstechnik. Sie ist gewebeschonend und gibt die Möglichkeit, sich rasch über den jeweiligen Status zu orientieren.

Die Mikropräparation der Cochlea wurde zum ersten Mal von Neubert (1900) angegeben. Wir haben dieses Verfahren modifiziert und erweitert, seit 1954. Auf ihm basieren unser Cytocochleogramm, das die statistische Sicherung der morphologischen Befunde ermöglicht, sowie unsere Gefrierpräparation der Schnecke zur Gewinnung kleinster Peri- und Endolymphportionen. Die Technik der Mikropräparation ist bisher nirgends klar und verständlich publiziert. Da wir diese Methode aber für ein wichtiges Verfahren zur Untersuchung der Strukturen des Innenohres ansehen, halten wir es für notwendig und gerechtfertigt, unsere langjährige präparatorische Erfahrung zusammenfassend darzulegen. Sie wurde vorwiegend an der Cochlea des Meerschweinchens, daneben auch an der des Kaninchens, der Ratte und des Menschen gewonnen.

### A. Mikropräparation der Cochlea

#### 1. Cortisches Organ

Da günstige Körpergewicht für Meerschweinchen, deren Cochlea mikropräpariert werden soll, beträgt etwa 200 g. Die Tiere werden sofort nach Versuchsende mit dem Ampulationsmesser oder bei kleineren Tieren, mit einem Scherenschlag getötet. Vom Foramen occipitale magnum aus lassen

sich beide Schnecken mit der Schere in 1-2 Minuten aus dem Schädel herauslösen und in die Fixationslösung einbringen. Luftblasen werden aus der eröffneten Bulla sorgfältig entfernt. Zur Fixation — sie erfolgt bei Zimmertemperatur — hat sich bei uns die Bouinsche Lösung, die jedesmal frisch angesetzt werden muß, am besten bewährt. Nach 24 Stunden werden die Schnecken aus der Fixationslösung herausgenommen und in 10% igem Alkohol ausgewaschen. Versuche mit supravitaler Fixation ergaben keine besseren morphologischen Bilder.

Zunächst werden die die Bulla umgebenden Weichteile sowie die knöchernen Wände mit der Schere so weit entfernt, daß die Cochlea noch gut zwischen Daumen und Zeigefinger gehalten werden kann. Falls einmal dabei die Schnecke zu sehr aus dem Felsenbein herausgesprengt werden sollte, läßt sie sich leicht auf einem kleinen Gipsblock befestigen. Wir halten es für wichtig, daß die Cochlea während des ganzen Präparationsvorganges in der Hand gehalten wird und nirgends fest fixiert ist. Denn nur durch die uneingeschränkte Bewegungsmöglichkeit ist ein optimales Arbeiten gewährleistet. Zu Beginn der Präparation fräsen wir unter der Präparierlupe bei 10facher Vergrößerung mit einem feinen Rosenbohrer die knochenartige Leiste an der Hinterwand ab, mit der die Cochlea mit dem Felsenbein in Verbindung steht. Anschließend wird mit dem Feinierer die Knochenkapsel der medialen Wand so weit abgeschliffen, daß das Ligamentum spirale in allen Windungen durchschimmert. Ein Abschleifen der lateralen Schneckenkapsel ist nach unseren Erfahrungen nicht erforderlich, denn sie stellt nur eine dünne, leicht abzulösende Lamelle dar.

Für den weiteren Verlauf der Mikropräparation sind nun Vergrößerungen 25- und 50fach zweckmäßig. Nach Abschieben der restlichen, die Schnecke deckenden Mittelohrschleimhaut wird zunächst an der Schneckenapfel ein kleines Loch mit einem feinen Häkchen eingebracht (Abb. 1). Von dieser Lücke aus erfolgt dann mit dem Häkchen das Abheben des dünnen Knochens über dem Ligamentum spirale, so daß dieses zur Darstellung kommt (Abb. 2). Dabei ist es sinnvoll, die geronnene Lymphe auszuspielen und die Schnecke mit Hämatoxylin oder mit Methylblau leicht anzufärben. Die Strukturen werden dadurch im Detail deutlicher sichtbar.

Die Präparation erfolgt also von der Spitze her, wobei wir bestrebt sind, den Modiolus stehenzulassen. Nach Abtragen der knöchernen Kapsel stellt sich das Ligamentum spirale dar und wird ebenso wie die als zarte Netzstruktur erkennbare Reißnersche Membran mit einer feinen Lanzette abgenommen. Noch besser als eine angeschliffene Lanzette haben sich zur Präparation der häutigen Teile kleine Rasterklingsplittter z. B. in feinen Gefäßklammern fixiert, bewährt. Diese Splitter öfters erneuert, lassen eine sehr sorgfältige und saubere Präparation zu. Nun wird die Membrana tectoria vom Cortischen Organ abgehoben und vor uns liegt die Basilarmembran mit dem Cortischen Organ (Abb. 3). Sie wird vom Modiolus abgetrennt und in Stücke geteilt, die jeweils  $1/2-1/3$  Schneckenwindung entsprechen. Dieses Unterteilen des Cortischen Organs erfolgt immer an



Abb. 1 Beginn der Mikropreparation der Cochlea. Ein Stäbchen der knöchernen Schneckenkapsel ist entfernt und das Ligamentum spirale der 4. Windung benachbart.

Abb. 2 Weiterer Schritt der Mikropreparation. Nach Entfernung der Kapsel der Cochlea liegt das Ligamentum spirale der Spitzenwindung frei. Der dunkle Streifen ist präpariert der pigmentreichen Sarsenularis.

Abb. 3 Basalmembran der 4. Schärfe nach Entfernung des Ligamentum spirale. Ein kleines Stück am Übergang der 2. zu 4. Windung ist bereits entfernt.

Ganzpräparat und nicht isoliert in Flüssigkeit. Jedes Stückchen der Basalmembran wird nun in ein vorbereitetes und nummeriertes Töpfchen mit Farblösung eingelegt.

Neben unserem Präparationsmikroskop liegt stets ein Schneckenschema, getrennt für die rechte und linke Seite. In dieses Schema wird die Topographie aller abgetrennten Teile sorgfältig eingetragen, um die spätere Auswertung zu erleichtern. Ebenso werden auch eventuelle Beschädigungen der Basalmembran hier vermerkt. Auf diese Weise wird Windung für Windung präpariert und registriert. Am Ende steht nur noch der Modiolus. Aus ihm läßt sich nun das Ganglion spirale isolieren.

## 2. Ganglion spirale

Nach der Präparation des Cortischen Organs steht nur noch die Schneckenkapsel mit der Lamina spiralis ossea sowie Teile der knöchernen Zwischenwände, welche die einzelnen Windungen voneinander trennen. Die letzteren werden entfernt, so daß sich nur noch die Lamina spiralis ossea um den Modiolus windet. Diese wird durch die Fissura spiralis in 2 Blätter geteilt, wobei das obere vestibuläre recht dick das untere, tympanale nur dünn ist. Weiter zur Schneckenachse hin liegt das Ganglion spirale im Rosenthalischen Kanal, einem Hohlraum, der durch das Auseinanderweichen der beiden knöchernen Blätter gebildet wird. Beginnend an der Spitze des Modiolus wird nun mit einer feinen Lanzette in die Fissura spiralis eingegangen und der Knochen vorsichtig in kleinen Stück



Abb. 4. Stadien der Mikropräparation des Ganglion spirale. 1. Mittels einer feinen Lanzette Abbrechen der oberen Knochenlamelle des Rosenthalschen Kanals, die bei 2 schon teilweise entfernt ist. 3. Nach völligem Abtragen des oberen Blattes folgt die Wegnahme des unteren. 4. Herausnahme des Ganglionswulstes. Die gestrichelte Linie zeigt die Abtrennung von den Fasern des N. cochlearis an.

chen abgebrochen (Abb. 4). Zweckmäßig beginnt man dabei zunächst mit der Entfernung des oberen Blattes und präpariert dann die dünne Knochenlamelle unterhalb ab. Um Artefakte zu vermeiden muß die Spitze der Lanzette beim Abbrechen beider Blätter immer am Knochen bleiben, wodurch ein Eindringen in das Nervengewebe verhindert wird.

Nach Entfernen des Knochens liegt das Ganglion frei und stellt einen dicken Wulst dar, der sich spiralig um den Modiolus windet. Der Wulst hängt nur noch an den zum N. cochlearis ziehenden Fasern. Diese werden sorgfältig durchtrennt und das Ganglion wird herausgenommen, wobei es wegen der Brüchigkeit des Gewebes selten gelingt, mehr als eine halbe Windung zusammenhängend zu entfernen. Da die Windungen des Ganglion im Vergleich zu denen der Basilarmembran wesentlich enger sind, ist ein solches Ganglionstück verhältnismäßig klein.

Die Mikropräparation der Cochlea anderer Säugetiere und auch der des Menschen wird im Prinzip auf gleiche Weise durchgeführt. Da aber die Schnecke bei vielen ähnlich wie beim Menschen im Felsenbein eingebettet liegt, muß die Entnahme der Cochlea bzw. des Felsenbeins aus dem Schädel den anatomischen Relationen angepaßt werden. Bei der Präparation selbst ist ein Vielfaches an Zeit erforderlich, da das Abfräsen der dicken Knochenlage, die die häutige Cochlea umgibt, sehr langwierig ist. Die Weichteilpräparation erfordert dann keinerlei besondere technische Kniffe mehr.

### 3. Histologische Bearbeitung

Die mikropräparatorisch gewonnenen Stücke der Basilarmembran können nun den einzelnen Färbungen ähnlich wie Gefrierschnitte unterzogen werden. (Selbstverständlich ist es auch möglich, die ganze Schnecke nach abgeschlossener Fixation zunächst zu färben und dann die Präparation anzuschließen.) Jedes nummerierte Basilarmembranstückchen muß dabei für sich bearbeitet werden. Auf Grund der geringen Größe und der Empfindlichkeit der Präparate ist zu ihrer Schonung zu empfehlen, diese in Hohl-



schliff-Objektträger zu bringen und mit einer feinen Pipette die Lösungen zuzugeben bzw. abzuziehen, so daß die Gewebestücke nicht immer wieder berührt werden müssen. Nach Beendigung des Färbeprozesses erfolgt die Entwässerung in aufsteigender Alkoholvereie bis zum 96%igen Alkohol. Von dort werden die Stücke in Terpineol gebracht. Diese Lösung macht die Stücke geschmeidig, heilt sie auf und verhindert eine Schrumpfung, so daß genügend Zeit bleibt, die Präparate vor dem Eindecken sorgfältig und eben auf dem Objektträger auszubreiten. Xylol haben wir wegen der Schrumpfungsfahr vermieden.

Die Stücke des Ligamentum spirale sowie die des Ganglion spirale sind im Gegensatz zu den Sektoren der Basilarmembran relativ dick und zeigen einen wenig geordneten Aufbau, so daß eine Verwertung als Ganzpräparat wenig sinnvoll ist. Die einzelnen Zellen überlagern sich dabei derart, daß die feineren Strukturen und deren Veränderungen nicht sichtbar werden. Wir haben deshalb die Präparate stets eingebettet und in dünne Schichten geschnitten.

### B. Das Cytocochleogramm

Schon bei unseren ersten Beschallungsversuchen hatten wir begonnen, die gesamte Cochlea durchzumikroskopieren, die Zahl der Kerne in der Relation normal geschädigt anzuzählen und sie in Schneckenschemata einzutragen (Beck, 1954, 1956). Eine exakte statistische Auswertung erfolgte jedoch damals noch nicht. Auf Anregung von Terayama verwenden wir nun für die statistische Auswertung seit längerem folgendes Prinzip.

In das vorher beschriebene Schneckenschema werden 24 Zählpunkte markiert (Abb. 5). Da nun jedes Basilarmembranstückchen in das Schema genau eingezeichnet wurde, läßt sich jeder Zählpunkt auf dem mikroskopischen Präparat ebenfalls genau bestimmen. Die Lage des runden Fensters dient dabei als Bezugspunkt. Bei der mikroskopischen Auswertung werden zu jedem Zählpunkt mindestens 100, meistens 200 Zellen ausgezählt. Aus dieser Zahl wird der Prozentsatz der veränderten zu den unveränderten Zellen bestimmt und in die darunterliegende Tabelle sofort eingetragen. So lassen sich innere und äußere Haarzellen getrennt voneinander auswerten, ebenso wie Schwellkerne, Kernpyknoten, Plasmaveränderungen und ähnliches. Die gewonnenen Zahlen werden statistisch ausgewertet und in kurz dargestellt (Abb. 6). Das auf diese Weise entstandene Cytocochleogramm der Schnecke erlaubt jetzt eine genaue statistische Auswertung und so eine Korrelation der morphologischen mit anderen, z. B. elektrophysiologischen Untersuchungsmethoden.

### C. Gewinnung der Innenohrflüssigkeiten

Mit Auswertung unserer Experimente trat zwangsläufig die Frage auf, wie erhält sich die Innenohrflüssigkeit nach akustischer Belastung oder nach Einwirkung ototoxischer Pharmaka. Da Untersuchung vor allem der

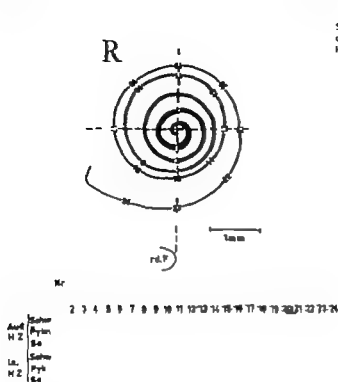


Abb. 5.

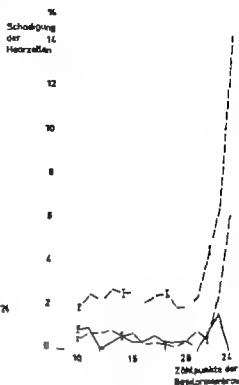


Abb. 6

Abb. 5 Formblatt des Cytoschilogramma. Im oberen Schema wird die genaue Lage der einzelnen Häutchenpräparate eingezeichnet, in das untere werden die Prozentzahlen der veränderten Haarzellen in den einzelnen Zählpunkten eingetragen. Die Auswertung erfolgt getrennt nach äußeren Haarzellen (Aß HZ) inneren Haarzellen (In HZ). Gewertet wurden Schwellkerne (Schw) Kerapyknosen (Pykn) und die Mitosen beider (Sa).

Abb. 6 Beispiel der statistischen Auswertung morphologische Veränderungen im Cortischen Organ. Jede Kurve zeigt den Durchschnittswert von 10 Meerschweinchen in Ordinate Zählpunkte auf der Basilarmembran (vgl. Abb. 5) Abszisse Prozentzahl der geschädigten Zellen. — Kontrolltiere — — — Tiere, die 10 Tage 250 mg Streptomycin-Sulfat pro die i.m. erhalten hatten — — — gleiche Streptomycin gegeben in Ozothin statt in Aqua d. st.

Eiweiß- und Ribonucleinsäurestoffwechsel interessiert hatte erschien es am sinnvollsten das Verhalten der Eiweiße auch in den Lymphen zu überprüfen. Zur Untersuchung kleinster Lymphproben war dabei die immunoelektrophoretische Darstellung, für ihre Gewinnung die Gefrier-Präparation am zweckmäßigsten (Beck & Holz, 1965). Da uns eine Kühlkammer nicht zur Verfügung stand haben wir folgenden Weg gewählt (Holz, 1964).

Die aus dem Schädel herausgelösten Schnecken der Meerschweinchen wurden sofort in flüssiger Luft eingefroren und auf einem Mikrotom montiert. Mit Hilfe eines von uns selbst gebauten Kryostaten läßt sich die Temperatur der Schnecke auf  $-10^{\circ}\text{C}$  halten so daß unter 25- bis 30-facher Vergrößerung ohne Gefahr des Auftauens die Schnecke präpariert werden kann. Mit zugeschliffenen Zahnsonden wird zunächst ähnlich wie oben für die Häutchenpräparation dargestellt der Knochen entfernt (Abb. 7a). Darunter liegen die gefrorenen häutigen Strukturen der Cochlea sowie die



Abb. 7 Gefrierpreparation der Cochlea. a. Beginn der Präparation. Schnecke *g* (frozen). b. Ein Stück der Knochenkapsel der Basalwindung ist entfernt. Darauf ist die *g* (frozen) Perilymphe (1) und das Ligamentum spirale (2) sichtbar.

gefrorenen Lymphen (Abb. 7 b) Gewebe und Lymphen können dabei gut voneinander isoliert werden. Erkennt man als Folge der Dekapitation Blutbeimengungen in der Lymphe, so wird die Schnecke sofort aus dem Versuch genommen. Ohne Zeitverlust und unter relativ guter Sicht lassen sich etwa 2 l Perilymphe in Form kleinster Gefrierstückchen mit der Lanzette an der Basalwindung gewinnen. Um genügend große Mengen von Endolympe für die Immuno-Elektrophorese zu erhalten sind Sammelproben aus verschiedenen Windungen notwendig. Die gefrorenen Lymphportionen werden nach Entnahme sofort auf die für die Immuno-Elektrophorese vorbereiteten Objektträger gebracht.

Das Gehäuse des selbstgebauten Kryostaten (Abb. 8) stellt ein gut isolierter Karton dar. An den Seiten finden sich 2 mm tiefe Öffnungen für die Hände. Außenmaße des Kartons: 41 × 41 × 41 cm. Innenraum: 20 × 12 × 10 cm.

Auf dem abnehmbaren Deckel wird ein Loch mit einem Durchmesser von 14 cm herausgeschnitten, so daß ein genügend große Beobachtungsluke für die Präparierlupe vorhanden war. Zum Schutz gegen Wärmestrahlung wurde die Öffnung mit einem Doppelfenster aus einem Glas verschlossen. Die Lupe befindet sich, fixiert an einem Stativ, außerhalb des gekühlten Raumes und ihr Objektiv stützt man Fenster auf. Auf dem Boden des Kartons sorgte ein mit flüssigem Stickstoff gefülltes 1/2 Liter Dewar-Gefäß für die nötige Kühlung. Das Dewar-Gefäß erhielt einen eisernen Deckel, dessen Bohrung den Sockel mit der aufgefrorenen

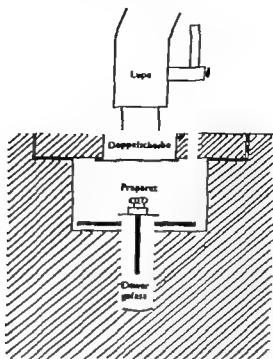


Abb. 8 Schematische Darstellung des selbstgebauten Kryostaten zur Gefrierpräparation.

Schnecke aufnehmen konnte. Der Metalldeckel hatte einen angeschweißten Eisenstab, der in den flüssigen Stickstoff tauchte und so die durch die Mikroskopleuchte entstandene Wärme ausreichend ableitete. Die Temperatur betrug bei dieser Anordnung  $-8^{\circ}$  unmittelbar auf dem Block unter  $-10^{\circ}$  bei normaler Raumtemperatur. Lederhandschuhe schützten die Hände vor Kälteschäden. Der Abstand Lupe-Objekt richtete sich nach dem Arbeitsabstand der verwendeten Präparierlupe.

Die immuno-elektrophoretische Aufschlüsselung der Lymphproben erfolgte auf dem kleinen IKB-Gerät nach der üblichen Methode (Einzelheiten s. bei Beck & Holz, 1960). Zu bemerken ist, daß wir mit käuflichen Antisera zunächst keine guten Erfahrungen machten und dazu übergegangen sind, eigene Antisera herzustellen. Als Tierspezies für das Anti-Meerschweinchenserum eignete sich dabei das Kaninchen besser als die Ratte. Nach etwa 4–6 wöchentlicher Sensibilisierung der Kaninchen ließen sich gute Meerschweinchen-Antiserum-Titer nachweisen, die erheblich höher waren als diejenigen der käuflichen Sera.

#### DISKUSSION

Seit 1954 wird von uns an der Cochlea die Mikropräparationstechnik durchgeführt. Sie hat sich im Laufe der Jahre ständig erweitert und verbessert für morphologische und modifiziert auch für biochemische Untersuchungen bestens bewährt. Wir haben deshalb jetzt die technischen Details, die bislang nirgends eingehend beschrieben sind, auf Grund un-

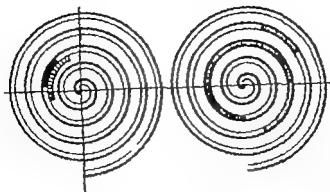


Abb. 9.

Abb. 10.

Abb. 9. Lage und Ausdehnung des ergriffenen Sektors der Basilarmembran nach Stimulusbeschallung 500 Hz und (IIIIII) 80 dB bzw. (IIIIII) 90 dB. Beschallungsdauer 2 min 30 sec

Abb. 10. Ausdehnung der Zellveränderungen (I der Basilarmembran nach einer Beschallung mit 500 Hz, 110 dB, 1 min 30 sec beim Meerschweinchen, das sehr empfindlich gegen Tonbelastung ist. Die kleine Areal im mittleren Drittel der 2. Windung zeigt die Lokalisation der vorübergehenden Veränderungen, die durch die unregelmäßigen Abstände sind. (Hier die 2. Harmonische bei 1000 Hz.)

seiner Erfahrungen zusammenfassend dargestellt. Die Methode hat neben der Gewissmachung den Vorteil, daß die Ergebnisse rasch vorliegen und auch rasch eine statistisch gesicherte Auswertung der morphologischen Befunde möglich ist.

Eine statistische Auswertung von Veränderungen der Cochlea wird von uns schon seit langem vorgenommen (Beck, 1955; 1956) und wir legen bei der morphologischen Untersuchung immer besonderen Wert darauf, daß stets die ganze Schnecke erforscht wurde. Die Notwendigkeit der Untersuchung der ganzen Cochlea zeigt z.B. Abb. 9 auf der die Areale der Basilarmembran eingetragen sind, die nach einer Tonbelastung mit 500 Hz morphologische Veränderungen zeigten. Diese Abschnitte konnten nur durch Präparation auch der dem Felsenbein anhaftenden Seite der Cochlea aufgedeckt werden. Noch deutlicher zeigt sich diese Notwendigkeit der Bearbeitung der ganzen Cochlea in Abb. 10 auf der die von uns 1960 aufgezogenen morphologischen Veränderungen des Cortischen Organs im Bereich der Harmonischen bei intensiver Tonbelastung mit 500 Hz eingetragen sind. Sie ließen sich nur durch die Bearbeitung der ganzen Basilarmembran nachweisen. Eine Auswahl des zur Untersuchung und Auswertung kommenden Materials der Cochlea z.B. aus präparatorisch-technischen Gründen erfahrungsgemäß ist ja die in die Bulla hineintragende Seite der Cochlea am leichtesten zu präparieren — kann so niemals den Anforderungen einer exakten morphologischen Untersuchung gerecht werden.

Aus dieser Erfahrung und den Forderungen, exakte statistische Daten

zur Korrelation verschiedener Untersuchungsmethoden der Cochlea zu erhalten (Stange *et al* 1966) entstand unser Cytocochleogramm das die detaillierte statistische Auswertung der Zellen des Cortischen Organs und ihrer Veränderungen gestattet. Wir haben so die Möglichkeit rasch die Ergebnisse verschiedener Untersuchungsmethoden zu korrelieren und damit umfassendere Aussagen über die Funktion der Cochlea zu erhalten. Die Mikropräparation gestattet weiter eine einwandfreie Gewinnung von Labyrinthliquor. Die Präparationstechnik muß dabei zwar etwas variiert werden, doch ist dies bei Kenntnis der Grundprinzipien der Mikropräparation ohne Schwierigkeiten möglich. Auf Grund unserer Erfahrungen halten wir so die Mikropräparation für eine äußerst wichtige Methode zur Untersuchung der Cochlea bzw. des gesamten Innenohres.

## SUMMARY

Exact description of the micropreparation of the cochlea. It allows an exact and quick representation of the organ of Corti, the spiral ligament with the stria and the spiral ganglion and their morphological variations. A cytocochleogram guarantees the statistical interpretation of the morphological results. Further it is possible to gain very small portions of perilymph and endolymph with this technique. Thus the micropreparation represents a very important method in investigating the cochlea.

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## LOSS OF HEARING FOLLOWING THE SYNDROME OF VAN DER HOEVE-DE KLEYN

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Osteogenesis imperfecta, often called the syndrome of Van der Hoeve-de Kleyn consists of blue sclerae fragilitas osseum and hardness of hearing. Previous authors have considered the impairment of hearing to be due to and identical with, otosclerosis. But in recent years some authors have questioned this opinion. The author presents four cases in which a stapes mobilization was performed in the ears.

The combination of the symptoms, blue sclerae osseous fragility and impaired hearing, is well known. According to Bigler (1923) it was first mentioned in 1922 by Dighton—and a little later (1917) by Brunson as well as by Frazer.

The combination is nevertheless often called "Van der Hoeve-de Kleyn's syndrome" after a publication (1918) in which the authors describe two Dutch families. In these families they detected one or several of the above mentioned symptoms in a large number of the families members.

Later the syndrome has been discussed by several authors. Rutlin (1922), Nager (1922), Bigler (1923), Gimpfinger (1926), Brickley (1941), Fowler (1949), Lindsay (1950), Bryan *et al* (1956) and Sooy (1960).

It is also mentioned in textbooks Jackson & Jackson, *Diseases of the Nose Throat and Ear* (1948), Nylen, Andersen, Loegaard & Kirila, *Nordisk Lærebok i Oto-Rhino-Laryngologi* (1958) and Coates, Schenk & Miller *Oto-Laryngology* (1960).

In Scandinavian literature there are communications by Felnes (1949), Hernberg (1952), Berfenslam and Smårs (1956) and Herberts *et al* (1963).

According to Bigler both Brunson and Frazer considered the impairment of hearing in cases of blue sclerae and osseous fragility to be due to otosclerosis. The same opinion is held by Van der Hoeve-de Kleyn and by the majority of later authors.

The basis for this opinion appears to be limited to purely clinical data. In the first place the nature of the impairment of hearing is found by the majority to be mechanical (conductive).

Histological observations of localized osseous changes in the area around the foramen ovale, as seen in otosclerosis, have been made in only 2 cases according to the available literature (Rutlin, 1922; Ogilvie, 1920).

It is postulated, however lately by Simon-Hall & Ogilvie, that the histological picture in osteogenesis imperfecta and otosclerosis generally has so

many traits in common, especially concerning the osteoblasts, that this must be an expression of a common etiology.

Altmann opposes this and emphatically declares that there is no support for this assumption of a common basic etiology in the available histological data.

Nager is also said to have found otosclerotic changes in the temporal bone from patients with Van der Hoeve-de Kleyn's syndrome. This appears, however, to be only partly true. Nager on numerous occasions has declared his agreement with the theory of a close connection between osteogenesis imperfecta and otosclerosis. His personal contribution, however, to support this opinion seems to be limited to the finding of an otosclerotic bone focus in a temporal bone from a patient with blue sclerae—but without any osseous fragility.

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At the Rikshospital in Oslo our interest in this syndrome of Van der Hoeve-de Kleyn was aroused during the autumn of 1960 when we were able to operate on 2 cases—and in both found anomalies of the stapes which did not seem to have been observed earlier.

Going through our archives two more operated cases were found of which one almost certainly and the other possibly demonstrated the same anomalies. The identity of these changes, however, were not at that time acknowledged.

The four cases were discussed in the Norwegian Oto-Laryngological Association in November 1960.

In addition I have quite recently been able to operate the other ear of one of these patients—and found the same changes in the stapes. The cases will be briefly discussed.

*Case 1* 41-year-old female. Several of the nearest relatives had blue sclerae, repeated fractures and impaired hearing. The patient also showed blue sclerae and as a child had two fractures. There had been buzzing in the ears and loss of hearing from the age of 20.

There was mechanical (conductive) impairment of hearing, symmetrical in both ears, which might well be consistent with otosclerosis.

Stapedolysis was performed. After loosening of the ear drum, the stapes appeared. It was palpated with a probe and was not fixed but unusually mobile. The mobility, however, was limited to the capitulum and the adjacent parts of the crura while the stapedial plate remained immobile.



The cause of this was that the crura in the area adjacent to the plate were degenerated into thin threads of connective tissue, in part adherent to the facial nerve.

These thin threads of connective tissue were then removed and likewise the rest of the crura with the capitulum. The plate now appeared normal. No otosclerotic changes were found either in the plate or in the adjacent bone.

Fenestration performed at a later date did not give any hearing improvement. The removed part of the stapes was found to be pathologic as the capitulum and the crura were unusually slender.

In the area of the capitulum and the collum two cavities were found lined with the epithelium of the normal middle ear.

Both crura were irregular. At the end of one a small necrotic area was seen (Fig. 1).

*Case II* 47-year-old male. He had one child, a daughter 15 years old, with blue sclerae, repeated fractures, but good hearing ability.

The patient had blue sclerae and had repeated hospitalizations on account of fractures. Buzzing was present in the ears, and his hearing was gradually declining from the age of 36. On admission there was a substantial loss of hearing of a mainly mechanical type. Stapedolysis was performed.

When the ear drum had been loosened, the stapes was clearly visible. It was found to be unusually mobile and on close inspection both crura in the area of the plate were found to have degenerated into fibrous threads. The capitulum and the adjacent parts of the crura were removed. The plate had a normal appearance. It was perforated at a single point and seemed to be of normal thickness. Neither the plate nor the adjacent area showed any structural changes which might suggest otosclerosis.

Fenestration at a later date did not result in any improvement of hearing ability.

The removed parts of the stapes showed the same curious characteristics as in Case I.—Cavities lined with epithelium within the area of the capitulum and collum—and deformed and structurally altered crura (Fig. 2).

*Case III* 33-year-old female.

A number of the nearest relatives were suffering from the syndrome of Van der Hoeve-de Kleyn. The patient had blue sclerae and numerous fractures.

There had been buzzing in the ears and loss of hearing from the age of 26.

On admission (Sept. 38) there was considerable loss of hearing, mainly of a conductive type as is common in otosclerosis.

Mobilization of the stapes in the left ear was performed. When the ear drum had been loosened the stapes was found to be quite mobile as far as the capitulum and the adjacent parts of the crura were concerned. The plate, however, did not accompany the movement. In the records describing

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stapes and the crura were particularly mobile, which was presumably due to an unintentional fracture during the operative procedure.

The fenestration was completed in the usual way with a modest improvement of hearing ability as a result.

*Case I* The right ear of *Case III* On admission (March 1964) there was still a predominant hearing loss of the conductive type symmetrical in both ears. If the findings proved to be the same as in the other ear it was planned to implant a polyethylene strut between the incus and the plate.

When the ear drum had been loosened an unusually mobile stapes was again found.

As in the previous case, the stapedia plate did not accompany the movement, on account of the crura being degenerated into fibrous threads.

The capitulum and crura were removed. The plate and the surrounding bone were of normal appearance.

A polyethylene strut was placed between the plate and the lenticular process.

This installation proved easy but did not lead to any improvement of hearing, the reason being that the strut was obviously too short. It was removed and replaced by a longer one, but during this process the plate loosened and became displaced half way into the labyrinth.

Obviously the plate had been very loose and since it was now out of function it was removed.

A piece of fat was placed in the open fenestra ovalis and a polyethylene strut (*ad modum* Shea) was placed with the pointed end on the fat and the other end around the process. The result was a considerable improvement of hearing ability which was also present when controlled six months later.

The removed part of the stapes showed the same anomalies as previously mentioned—a delicate, slightly deformed crura and epithelium-lined cavities in the area of the capitulum and collum. In addition to these observations, one is reminded that both Sooy in four cases and Herberts *et al* in one case found what we call a mobile stapes. Their findings are not described more precisely but it would seem reasonable to assume that these might be the same anomalies as in our cases.

## DISCUSSION

From an otological point of view the widespread interest in the syndrome of Van der Hoeve-de Kleyn is possibly due to the presumed connection between otogenesis imperfecta and otosclerosis, which might throw some light upon the pathogenesis of otosclerosis.

Strictly speaking, only Rutlin's and Gimplinger's cases from 1922 and 1926 can represent any arguments for a connection.

In both reports osseous changes were seen to be localized to a limited



FIG. 1 Stapes, case 1. Note the two epithelium lined cavities in the corpus.

FIG. 2 Stapes, case 2. Also here avulsed crura are seen in the corpus, and the crura are structurally altered.

the operation, the explanation was that the lack of accompanying movement of the plate obviously was due to some unusually slender flexible and delicate crura. The plate appeared normal. It was mobilized (i.e. loosened) from its surroundings, which was unusually easy.

The results was a spontaneous improvement of hearing but with a relapse to pre-operative status in a short time.

*Case IV* 44-year-old male. The patient's father had blue sclerae and innumerable fractures, but had good hearing into advanced age.

The patient had blue sclerae and repeated fractures.

There had been loss of hearing from the age of 40. On admission there was a relatively considerable loss of hearing predominantly of the mechanical type almost symmetrical in both ears.

The case was considered to be otosclerosis. Fenestration of the right ear was performed.

In the records from the operation it is emphasized that the head of the

factory results. These findings may be supported, while on the other hand considerable improvement of hearing was obtained by stapedectomy in one of our cases.

How these anomalies of the stapes have arisen can hardly be explained by our histologicals alone. Considering the nature of the anomalies and their uniformity from case to case, it seems reasonable to regard these as an expression of a generalized osseous disease—osteogenesis imperfecta.

This opinion is supported by the histological findings reported by Hall & Nahr in the Norwegian Oto-Laryngeal Society September 1962.

### ZUSAMMENFASSUNG

Osteogenesis Imperfecta, auch Van der Hoeve-de-Kleyn Syndrom genannt, wird durch blaue Skleren, Fragilitas osseum und Selbstverletzlichkeit gekennzeichnet. Früher haben mehrere Autoren die begleitende Schwerhörigkeit als in Resultat der Otitis media und war als otisch mit Otitis media betrachtet. In den letzten Jahren dagegen gibt es Autoren, die in welche Überlegung der Schwerhörigkeit bei Osteogenesis Imperfecta einen Bericht von der Fall ist, die an Osteogenesis Imperfecta leiden, an denen fünf Ohren mit Stapedeummobilisierung operiert worden sind.

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area in the stapes and the surrounding bone as is common in otosclerosis. However it seems obvious that these patients suffered from *osteogenesis imperfecta* and otosclerosis.

The interpretation of the histological picture seen in relation to the asserted conformity between the two diseases seems controversial. To quote Altmann

"Since bone tissue reacts in identical ways as a result of many different stimuli histological similarity or even complete likeness, does not necessarily tell us anything about the basic cause and thus nothing about a possible relationship

Likewise the presence of a conductive loss of hearing in the two diseases can in no way be interpreted as an expression of an intimate connection between the two

In our cases suffering from the syndrome of Van der Hoeve-de Kleyn part of the stapes crura were found to have degenerated into thin fibrous threads in four of their ears. In the fifth ear the same anomaly had possibly been present

Beyond doubt this anomaly can completely explain the conductive component in the patients' impairment of hearing. Thus the assumption of otosclerosis must be superfluous in these four possibly five ears, unless one would postulate that both a fibrous degeneration of the crura and an otosclerotic fixation of the plate existed, which seems unlikely

Moreover this is contradicted by the findings in Case no. V where the plate was obviously very loosely placed in the fenestra ovalis.

These four or possibly five ears naturally do not allow any conclusions about the cause of the loss of hearing in the syndrome of Van der Hoeve-de Kleyn generally. However it is justifiable to state that they represent serious reasons for doubting the validity of the present general opinion.

If Sooy's four cases and the single case of Herberts *et al* may be included—which seems justifiable—our reasons for doubt are still more strengthened. This sum of ten ears seems to be a considerable number when seen in comparison to Rutin and Gimplinger's two cases—and the fact that the syndrome of Van der Hoeve-de Kleyn must be considered a rarity.

In addition to this there is reason to doubt a connection between *osteogenesis imperfecta* and otosclerosis on purely clinical grounds.

Rutin proposed that the loss of hearing in several of his patients was due to *laesio cochlearis* as he expressed it, i.e. a neurogenous type of hearing loss. According to Clerc and Deumier the same observation was made by numerous authors later on—and we have also seen the sensorineural type of hearing loss in connection with blue sclerae and osseous fragility. Sometimes we have found a quite considerable loss of hearing down to complete deafness—which is unusual in otosclerosis.

In addition to this we must consider the fact that fenestration in the syndrome of Van der Hoeve-de Kleyn is reported to give rather unsatis-

## THE STAPES IN OSTEOGENESIS IMPERFECTA

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Referring to cases of osteogenesis imperfecta presented by Ophelm in the present issue the authors describe the histological findings in the stapes of a newborn suffering from this disease. It is demonstrated that the actual stapes was abnormal, its crura being fragile and incomplete whereas the footplate and its surroundings were normal, in contrast to the observations in otosclerosis.

Ophelm (1967) has compared the findings in osteogenesis imperfecta (also called the syndrome of Van der Hoeve-de Kleyn) and otosclerosis. From his report it is seen that histologic investigations in these cases are scarce and that, in view of his findings, the old conception of the two diseases being identical concerning the cause of the loss of hearing must be revised.

This syndrome includes blue sclerae, fragilitas ossium and hardness of hearing. Of course this triad, on account of its multifarious clinical manifestations, has inspired many to estigators, but despite the ample literature the etiology of the disease still remains obscure. The common assumption is that a dominant mutation must be present (Bauer 1920, Fuss, 1920 v. Seedorf 1949). The disease is classified according to its three different manifestations: osteogenesis imperfecta congenita, tarda gravis and tarda levis (Seedorf 1949). In the first congenital type the individuals usually die before their hearing can be evaluated. In the second and third types the patients become hard of hearing at about thirty years of age, which corresponds to the circumstances in otosclerosis. However in osteogenesis imperfecta the loss of hearing becomes more pronounced and cochlear or neural defects are usually involved. Thus, there is a divergence between the two diseases concerning the loss of hearing, as there are concerning the other characteristics.

Blue sclerae are reported in connection with otosclerosis in 60 per cent (Fowler 1952) but in connection with osteogenesis imperfecta in 95 per cent. The fragile skeleton is a dominant phenomenon in osteogenesis imperfecta, but is seen very seldom in connection with otosclerosis.

Supporting the view expressed by Ophelm that the two diseases are also essentially different concerning the middle ear, a case is presented in which histologic examination of the stapes was performed.

Our case was a newborn female with healthy parents and no cases of either osteogenesis imperfecta or otosclerosis in the family. The child was

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FIG. 1. Drawings of sections of the stapes. 10 microns. Every 10th section drawn. Magnification 28.  
1 a. 2. The stapes, med-line section.

An important objection, however to the validity of our assumption lies in the fact that these were preparation from a newborn, and the question then arises. At what age does the earliest stages of otosclerosis occur?

In the literature it is seen that Manasse (1915) found otosclerosis in a 3 year-old, and Culld (1930) states that otosclerotic changes may begin as early as the end of the first year of postnatal life. Thus it is an open question whether otosclerotic foci might have developed in the case of a survival, and whether it is possible to detect earlier foci.

born two weeks premature weight 2960 g, length 44 cm. The extremities were plump and X rays revealed multiple fractures in the arms, legs and costae. The calvarium was soft and its sclerae blue. However the nourishment of this child met with no difficulties and its weight was gaining until it acquired a fever and died of pneumonia on the 20th day of life.

At autopsy the lungs were found to be juvenile and stuffed, otherwise there were no pathological findings in the viscera including the parathyroid glands.

The appearance of its bony structure is of special interest.

The calvarium was soft, consisting mostly of connective and cartilaginous tissue. Multiple fractures were shown in the extremities and in the costae around both of which was a rich formation of callus.

The temporal bones were preserved in formaline and later decalcinated and sectioned. As a preparation of the cochlea was then out of question our interest concentrated on the middle ear especially the stapes and its surroundings.

The stapedia joints showed no abnormalities, and especially no otosclerotic foci. None of the localized patches of hyperplastic bony lamellae, heaps of osteoblasts and the great number of capillaries usually seen in otosclerosis were present. On the contrary the joints connecting the stapedia plate and the oval window were quite normal and no obliteration was found.

Thus in this case, where the clinical and pathological findings confirmed the diagnosis *osteogenesis imperfecta*, any resemblance to otosclerosis can be ruled out.

The fact that the footplate and its surroundings were found normal brought forth the next question: What about the structure of the stapes itself? And this brings us to the main point of our investigation. The pathological findings in the stapedia structure might if found in grown ups, explain a loss of hearing of the mechanical type.

The stapes was decalcified and the following paraffin cast sectioned and stained. Fig 1 shows a drawing of every 10th section and Fig 2 is a photograph of the stapes.

In the first place it seems obvious that this is not a normal stapes. The corpus is deformed, the crura frayed thin in some places thread like and the edges as seen in the photograph are irregular. In none of the sections were the crura found solid all the way; it is seen that one crus ends as a pointed tip towards another at the footplate with only a fibrous connection and the other is only seen as a thin fragile thread. These findings correspond with those referred to by Ophelm in his cases of *osteogenesis imperfecta*. In conclusion it may be stated that this stapes would have prevented the perception of sound due to its mechanical properties. The pathological findings, however, were not of otosclerotic nature as the footplate and its surroundings were quite normal whereas the stapedia crurae were abnormal, fragile, flexible, frayed and incomplete.

## BÉKÉSY TRACINGS IN NORMAL LISTENERS FOLLOWING CONTRALATERAL MASKING

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Békésy fixed-frequency tracings for continuous tones were studied in normal listeners before and after masking the contralateral ear with wide-band noise of low and moderate intensity. In many cases, the effect of contralateral masking persists beyond the masking period, and in some cases the effect is even more pronounced after the exposure to noise than during the exposure, excessive threshold drifts being observed. A weak masking of one ear is quite regularly followed by facilitation in the opposite ear and in this ear exclusively.

In our investigations of contralateral masking and Békésy audiometry by the method of Jerger in normal listeners, we found that masking of the non-test ear during the threshold recording resulted in the following changes: (1) Reduction in tracing amplitude in the fixed-frequency curves at 1000 and 4000 cps. This amplitude reduction was most pronounced in the continuous tone tracings (the C tracings) but the change was also well marked in the tracings recorded with interrupted tones (the I tracings). (2) Separation between I and C fixed frequency tracings at the frequencies mentioned. The separation was due to the reduction in the tracing amplitude of the C curve as well as to the fact that the threshold changes resulting from masking were greater for C than for I. The above changes can presumably be ascribed to the influence of masking on the adaptation characteristics of the test ear. In the investigations, the fixed frequency curves were recorded with masking for a period of 3 minutes. The effect of contralateral masking was observed to develop quite gradually: the tracing amplitude at 1000 cps, for example, was found to be noticeably smaller during the 3rd minute than during the 2nd minute. During the experiments, it was observed that the changes in the curves could persist after the noise was switched off.

The present investigation was made to evaluate the after-effect of contralateral masking. As in the previous investigations, the duration of each masking period was 3 minutes. Two situations were selected for investigation. In the first, the non-test ear was exposed to noise and the test tone

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Nevertheless, we found it of interest to observe that the appearance of the stapes in a newborn suffering from osteogenesis imperfecta was consistent with and an explanation of a loss of hearing

### ZUSAMMENFASSUNG

Auf vier Fälle von Osteogenesis imperfecta hinweisend (siehe Ophelms Artikel dieses Heftes) beschreiben die Autoren den histologischen Befund des Steigbügels bei einem Neugeborenen mit Osteogenesis imperfecta. Dieser Steigbügel ist abnorm mit fragilen und unvollständigen Schenkeln. Die Fussplatte und ihre Umgebung dagegen sind normal. Im Gegensatz zu den Befunden bei Otosklerose

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masking, the post masking tracing behaviour of the subject was always compared with the pre-masking behaviour in the session in question. The results were analysed both with regard to thresholds and to the mean number of pen swings per minute. The threshold values were determined for the last 10 seconds of each period of 1 minute, as the midline between tops and bottoms of the tracing excursions. The number of pen swings per minute gives the number of separate pen strokes (pen reversals) and is taken as a measure of the mean tracing amplitude, as the two values are inversely proportional.

## RESULTS

The effect of a preceding contralateral masking varied individually and even in the individual subject the effect was not constant. Thus, in experiment I the shifts in the same individual were not always in the same direction after masking levels of 70 and 90 dB and in experiment II, where the investigation with 90 dB masking was performed twice, the post masking tracing behaviour was not always the same in the two sessions.

### 1 Thresholds

Table 1 gives the results for experiment I. The threshold for continuous tone is indicated in relation to the subject's initial threshold for *I*. A statistical analysis by means of the *t*-test showed that the mean difference between pre- and post masking threshold levels did not differ significantly from 0. In one of the subjects, however marked shifts were found in

TABLE 1 Continuous tone thresholds in experiment I before and after contralateral masking

The above indicate differences (dB) between C thresholds and initial threshold for *I*. For *II* see the column that the threshold for *C* was found at higher sound pressure. The pre-masking determinations from the 1st and 2nd sessions are combined in the table

Test tone frequency	Before masking		After 70 dB masking		After 90 dB masking	
	End of 1st min	End of 2nd min	End of 1st min	End of 2nd min	End of 1st min	End of 2nd min
250 cps	Mean 0.7 Median 0.3 Range 8.0 to 8.5	Mean 1.8 Median 1.0 Range 11.0 to 10.0	Mean 1.8 Median 0 Range 2.0 to 18.0	Mean 0.3 Median 0 Range -7.0 to 10.0	Mean 2.3 Median 0.8 Range 5.0 to 14.0	Mean 2.9 Median 1.8 Range -2.0 to 12.0
1000 cps	Mean 2.1 Median 1.5 Range 2.0 to 7.0	Mean 2.8 Median 2.3 Range 1.5 to 12.0	Mean 2.9 Median 3.0 Range 1.0 to 12.5	Mean 5.2 Median 3.5 Range 0 to 16.5	Mean 2.2 Median 0 Range -7.5 to 21.5	Mean 3.2 Median 0.5 Range 7.5 to 24.0
4400 cps	Mean 4.5 Median 4.0 Range 2.0 to 18.0	Mean 6.0 Median 3.8 Range 0.5 to 19.5	Mean 4.3 Median 2.0 Range 1.0 to 21.5	Mean 8.6 Median 4.0 Range 7.0 to 48.0	Mean 5.3 Median 3.5 Range 3.0 to 21.0	Mean 6.5 Median 2.0 Range 1.5 to 29.0

was not introduced until immediately after the noise was switched off. In the second situation the subject was asked to trace his threshold during the exposure to the contralateral masking, and to continue tracing after the masking was switched off. Supplementary to the above, we examined whether in a 3 hour session in which the contralateral ear had been exposed repeatedly to masking fixed frequency curves recorded towards the end of the session differed from curves recorded at the commencement of the session. The curves for continuous tone were of particular interest, as the changes are most pronounced in these.

## PROCEDURE

The investigation comprised 10 normal listeners aged 18-23 years. Seven of them had taken part in the previous investigation of Békésy audiometry and contralateral masking, while the other 3 were given a practice session before the actual experiment. The apparatus used was as described previously: the calibration is now according to the ISO 1004 Standard. The test tone was delivered by ordinary headphone, the noise (wide-band white noise) by insert type receiver. The rate of attenuation was 120 dB/min. Each subject was examined in 2 sessions at an interval of about 3 weeks. All investigations were made at 4000, 1000 and 250 cps always in the order indicated. In spite of the risk of a time-order-effect, we chose to keep the sequence fixed in order to reduce the number of variables. The following investigations were made:

At the commencement of each session threshold tracings were made with interrupted and continuous tones for 2 minutes each. Then followed

### *Experiment I*

This experiment consisted of threshold measurements for 2 minutes with continuous tone after masking had been delivered to the contralateral ear for 3 minutes. In the first session 70 dB SPL was used, in the second session 90 dB.

### *Experiment II*

Here the subject traced his threshold during the masking period of 3 minutes. After the noise was switched off the subject continued to trace for 2 minutes. The experiments were performed at both 70 and 90 dB SPL during the first session. During the second session only a masking level of 90 dB was used.

Finally at the end of the session the threshold measurements for I and C were repeated for 2 minutes each.

All tracings were commenced from the level of inaudibility and the subject was allowed 15 seconds to find the threshold. These 15 seconds were not included in the calculations. In evaluating the influence of

TABLE 2. Continuous tone thresholds in experiment 11 in which the subject traced his threshold while contralateral masking was applied

The above again indicates the differences (dB) between the threshold level measured and the subject's initial threshold for *I* being positive when the threshold for *C* was the poorer. The 10 dB condition was instigated twice, and these measurements are combined in the table.

Test tone frequency	70 dB contralateral masking			90 dB contralateral masking		
	End of masking	End of 1st min	End of 2nd min	End of masking	End of 1st min	End of 2nd min
250 cps	Mean	2.0	1.8	0.6	3.2	2.5
	Median	0.5	0.3	1.0	2.0	-0.5
	Range	-4.0 to 15.0	-6.0 to 15.0	-3.0 to 9.5	-7.0 to 42.5	-8.5 to 33.5
1000 cps	Mean	8.4	7.0	6.4	10.3	7.4
	Median	3.3	4.3	4.0	9.1	4.3
	Range	1.0 to 13.6	3.0 to 22.0	3.0 to 26.3	-0.5 to 46.5	-3.5 to 38.5
4000 cps	Mean	12.0	12.3	12.4	12.1	9.6
	Median	8.8	4.0	5.3	11.9	9.5
	Range	1.0 to 38.0	2.0 to 53.0	0.5 to 47.5	>-30.0 to 45.0	1.0 to 51.0

threshold was -10 dB at the termination of masking period after masking the threshold improved further so that after the lapse of 2 minutes it was 20 dB better than the initial value for *I* and 23 dB better than average normal threshold.

A comparison of the tracings at the commencement and termination of the session gave the following results. At 1000 cps and 4000 cps, the separation between midpoints of the *I* and *C* tracings was on the average slightly less at the end of the session than at the commencement (at 1000 cps, the mean decrease was 1.2 dB, at 4000 cps it was 1.3 dB) at 250 cps the separation increased by 3.9 dB on an average.

### 2. Number of pen swings per minute

Experiment 1. Figs. 3a, b and c show the number of pen swings per minute after masking, in relation to the number before masking. The values

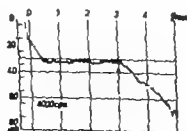


FIG. 4. Tracing from subject B. H. The contralateral ear was masked with 90 dB during the first part of the tracing. The masking was switched off at 1

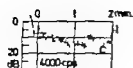


FIG. 1

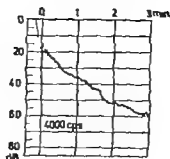


FIG. 2

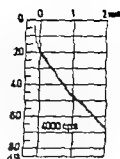


FIG. 3

FIG. 1 Pre-masking tracings for intermittent (*I*) and continuous (*C*) from subject S. H.

FIG. 2 *C*-tracing from the same subject recorded after exposure of the non-test ear to 0 dB wide-band noise for 3 minutes. The tracing in this case was followed longer than the usual two minutes, in view of its remarkable course.

FIG. 3 *C*-tracing recorded after contralateral masking of 60 dB intensity for 3 minutes. The curve was recorded during a third, supplementary session.

Figs. 1 and 2 the thresholds before and after 70 dB masking are shown. After exposure to 90 dB the change was less pronounced. This subject, S. H., was examined in an extra session in which 50 dB masking was used; the effect was striking (Fig. 3). These pronounced threshold drifts, which continued as long as the threshold was followed, were only found at 4000 cps. Subject S. H. is a 20-year-old medical student, in perfect health and with a completely negative anamnesis.

Table 2 shows the results for experiment II. The table gives the threshold value at the end of the masking period, and also 1 and 2 minutes after the cessation of the noise. As previously, the threshold values are indicated in relation to the subject's initial threshold for *I*. In the table, the results of the two experiments in which 90 dB masking was employed are combined. As will appear from the median values, shifts at 250 cps were usually small. At 1000 and 4000 cps, the threshold generally improved only gradually after masking was switched off, and without reaching the pre-masking levels of Table 1 completely. In two of the subjects, switching off the noise resulted regularly in a definite worsening of the threshold (7.5 to 38 dB), so that at times the curve did not stabilize in the course of the follow-up period. Fig. 4 shows the result for subject S. H.

A somewhat unexpected result was that at 4000 cps, the *C* threshold in one of the subjects gradually became more and more acute during contralateral masking of 90 dB. Thus, after 3 minutes the threshold was 25 dB better than the pre-masking threshold for *I*. On repeating the experiment, the threshold became > 30 dB better than the threshold for *I* (the attenuation of the audiometer being insufficient for the recording). On switching off the noise, the threshold was normalized on both occasions to within  $\pm 3$  dB. This subject was also examined in a 3rd session and here the



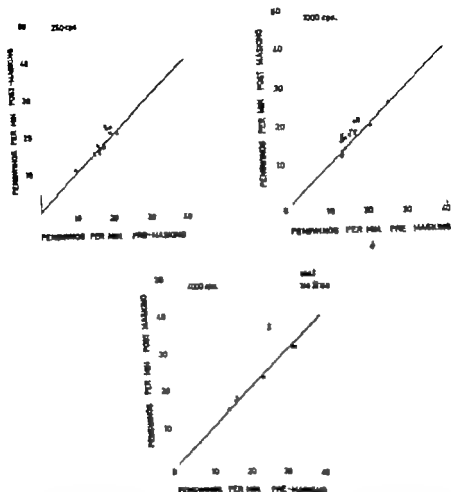
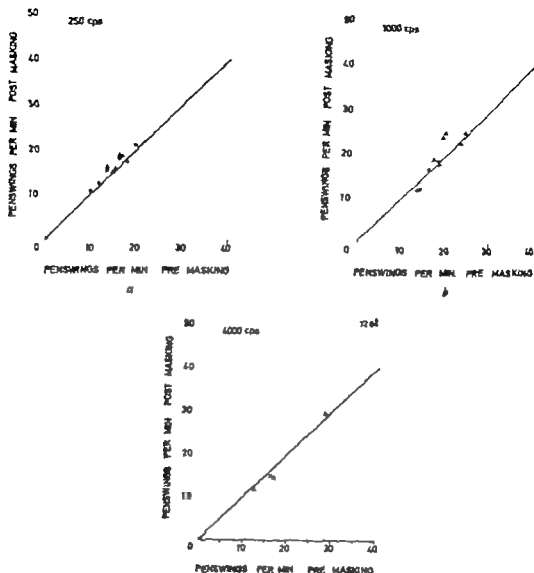


FIG. 8. a, b and c. The mean number of pen swings per minute measured over a period of 2 minutes after contralateral masking, in relation to the corresponding number before masking. Results from experiment II masking condition:  $\circ$ , 6 dB SPL;  $\Delta$ , 99 dB SPL (1st session);  $\bullet$ , 99 dB SPL (2nd session).

respectively. At 1000 cps, the mean increase was  $2.7 \pm 1.2$  and  $2.9 \pm 0.9$ , respectively, while at 4000 cps the mean increase was  $8.2 \pm 4.6$  and  $5.6 \pm 3.8$  pen swings per minute. As indicated by the asterisks, the mean values of the changes at 1000 cps were found to differ significantly from 0 at the 5% level. At 4000 cps the differences were not statistically significant.

Comparing the values at the start and at the termination of a session, no systematic variation was found. At 1000 cps and 4000 cps, the difference was very slight (an average of  $0 \pm 0.3$  and  $-0.4 \pm 1.4$ , respectively). At 250 cps, the difference was slightly greater:  $-1.4 \pm 1.6$  excursions per minute.



FIGS. 5 a b and c The mean number of pen swings per minute measured over a period of 2 minutes after contralateral masking, in relation to the corresponding number before masking. Results from experiment I. Masking condition: ● 70 dB SPL, ▲ 90 dB SPL.

are mean values for the complete 2 minute period. When the values for the 1st and 2nd minutes were plotted separately the same overall picture was obtained. According to the *t* test the mean change did not differ significantly from 0 either after noise at a level of 70 dB or 90 dB. Combining the data from both masking conditions the change at 1000 cps was  $1.3 \pm 0.9$  and at 4000 cps,  $1.8 \pm 2.5$  pen swings per minute.

In a corresponding manner Figs. 6 a b and c show the result from experiment II. At all 3 frequencies, there is a preponderance of observations above the 45° line i.e. the number of pen swings is increased after masking. At 250 cps, however, the mean increase in the number of excursions per minute amounted to only  $0.6 \pm 1.8$  and  $1.4 \pm 1.3$  after 70 and 90 dB masking,

body or to the auditory cortex. The threshold drifts observed in the present investigation are too great to be compatible with such a concept. Alterations must also occur at lower levels of the auditory pathways, presumably even in the cochlea. These alterations could be mediated through efferent fibres.

To sum up the present investigation, it may be said that masking of one ear is often followed by changes in the threshold function of the contralateral ear which persist for minutes. These changes are not a simple function of the exposure to noise, as in general they are only pronounced when the subject has traced his threshold during the masking period. In some cases, the changes are considerably greater after masking than during masking.

### ZUSAMMENFASSUNG

Man hat bei Normalhörenden die frequenzkonstanten Békésy Kurven für stetige Töne vor und nach der Maskierung des kontralateralen Ohres mit weißem Geräusch von niedriger und moderater Intensität untersucht. In vielen Fällen dauert der Effekt der kontralateralen Maskierung bis über den Zeitraum der Maskierung an, und in einigen Fällen ist die Wirkung sogar noch ausgesprochen — nachdem die Stimulation des kontralateralen Ohres zu Ende ist — als während derselben mit intensiven Schwankungen zur Folge. Eine ganz schwache Maskierung des einen Ohres wird regelmäßig von Sinuseln im gegenüberliegenden Ohr und zwar in diesem Ohr all in, gefolgt.

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Recd June 12, 1967

## DISCUSSION

In experiment I one of the subjects showed pronounced temporary changes in threshold after low level contralateral masking. The threshold drifts were of the same order of magnitude as those seen in patients with acoustic neuromas, but were observed only at 4000 cps. They were accompanied by a considerable reduction in tracing amplitude. The other subjects showed no definite effect. During this experiment two of the subjects noted tinnitus in the test ear on termination of the masking. In Thellgaard's investigations (1951) of auditory fatigue some of the subjects experienced a bilateral buzzing after unilateral stimulation. This never occurred unless the intensity of the stimulus (always a pure tone) was higher than 85 dB and a buzzing exclusively in the non-stimulated ear occurred in only 7 out of 214 experiments. In order to evaluate the phenomenon we exposed 10 normal listeners to 50 dB unilateral masking for 3 minutes after which the headphones were disconnected. I reported that after masking there was a faint seething or ringing sound in the non-stimulated ear. The sound gradually decreased but generally persisted for 30 to 40 seconds. None of the subjects experienced tinnitus in the masked ear. If 90 dB was applied the sensations were more variable.

In experiment II it was noteworthy that at 1000 cps and 4000 cps, two of the subjects had the most pronounced threshold changes after the masking was switched off. After masking at a level of 90 dB the threshold decayed in both subjects to 60–70 dB hearing level in the course of 2 minutes. For the rest of the group it was characteristic that the changes in threshold resulting from masking disappeared only gradually. In a previous study we showed that at 1000 cps and 4000 cps, the tracing amplitude is reduced by simultaneous masking of the contralateral ear. In the present investigation we found that measured over a period of 2 minutes the mean tracing amplitude at 1000 cps was smaller after masking than before. There is thus a pronounced tendency for the reduction to persist after the noise is switched off.

Among the after-effects to contralateral stimulation described by previous authors, the so called "hetero-lateral dip" ought to be mentioned. Following exposure of one ear to a pure tone of fatiguing intensity a dip may sometimes be demonstrated also in the non-exposed ear. This was described by Rawdon Smith (1935/1936), confirmed by Grelsen (1951) and by Thellgaard (1951) and more extensively studied by van Gool (1952). According to the last named author the heterolateral dip is always considerably smaller than the dip in the directly stimulated ear. It does not exceed 25 dB, and it cannot be produced in persons with complete one-sided deafness. In the Grelsen and van Gool studies an inverse reaction was noted in a few exceptional cases: after the stimulation there was a definite improvement of the threshold of the heterolateral ear. Van Gool ascribes the heterolateral dip to processes localized to the medial geniculate

## MATERIALS AND METHODS

Maxillary mucosa, mucosa of the inferior turbinate and nasal polyp were obtained by operation from patients with sinusitis. Examined specimens consisted of 11 cases of maxillary sinus mucosa, 10 cases of nasal polyps and 7 cases of mucosa of the inferior turbinate. These mucosa were added to one half of wet tissue weight of 0.1% cetyltrimethylammonium bromide solution. The mixture was homogenized and then centrifuged at 10,000 r.p.m. for ten minutes at 0°C. The supernatant was used for the experiment.

Electrophoresis and immunoelectrophoresis were performed using a 20 mm x 76 mm microscopio slide. A 1.5% agar solution prepared in veronal buffer pH 8.6, ionic strength 0.05 was used as a medium for electrophoretic separation. Two parallel round wells of 2 mm diameter were cut in the agar plate. For electrophoresis to analyze the fibrinolytic enzyme, these two wells were filled with the same sample. Electrophoretic separation was carried out for a period of 120 min at 6 mA per one plate coupled with veronal buffer at pH 8.6 with an ionic strength of 0.05 at 0°C. On completion of electrophoretic separation, a longitudinal cut was made in the midline of the agar plate, and one side of the cut agar was sectioned in 3 mm of its width. Then each section of agar was placed on the fibrin plate prepared by the method described below. Following this, fibrin plates were incubated for 18 hours at 37°C. After incubation the lysed zones were measured respectively. The other side of the cut agar was placed in a dry heat oven and after drying was stained with amido black dye for one hour. To remove excess dye it was washed with a solution of 5% glacial acetic acid.

For immunoelectrophoresis, the upper well was filled with the human serum and the lower well with the extract of nasal mucosa. After electrophoretic separation, a longitudinal trough 2 mm in width was cut out and filled with horse anti-whole human serum. The plate was placed in Petri dishes containing moistened filter paper and was incubated at 37°C for 24 hours to permit diffusion and reaction of the antigen-antibody system. This was washed for three days in phosphate buffered saline, pH 7.6, with changes twice daily of buffered solution. After this washing, the agar plate was washed two or three times an hour with distilled water and then heat fixed and stained by amido black dye. Bovine fibrinogen of Armour Laboratories was dissolved in a veronal buffer pH 7.4, making 0.2% solution. Yarkase streptokinase preparation of Lederle Laboratory and bovine thrombin (typical of Mochida Pharmaceutical's) was used. Nine ml of 0.2% fibrinogen solution was mixed with 0.3 ml of 100 units per ml thrombin in a Petri dish and a fibrin plate was made. In order to detect a streptokinase (Sk)-activated enzyme that is plasmin, 100 units of Sk were added to a Petri dish before forming the fibrin plate. Horse anti-whole human serum was kindly offered by the Department of Pharmacology of Nihon University School of Medicine Tokyo (Prof. M. Kobayashi).

## THE ELECTROPHORETIC ANALYSIS OF THE "NASAL FIBRINOLYTIC ENZYME"

Y SASAKI

*From the Department of Otorhinolaryngology Nihon University  
School of Medicine Tokyo Japan*

Nasal mucosa has a specific proteolytic enzyme which the author calls the "nasal fibrinolytic enzyme". In the work described in this paper the relationship between the nasal fibrinolytic enzyme and the SK activated enzyme in nasal mucosa and human blood serum was investigated by electrophoresis and immunoelectrophoresis. The nasal fibrinolytic enzyme was located in the neighbourhood of the  $\beta$ -globulin fraction. The SK activated enzyme in nasal mucosa was strongest in the  $\beta$  globulin fraction and in this respect is similar to human blood serum. The distribution pattern of the SK-activated enzyme in the nasal polyp was more closely related to the blood serum than other nasal mucosa. By immunoelectrophoresis it was found that the nasal polyp seemed to have more properties similar to blood serum than other nasal mucosa. The pathological and biochemical significance of the nasal polyp is discussed in the light of these observations.

Chronic sinusitis has a variety of features in clinical and pathological types, amongst which the nasal polyp is one of the characteristic products. It is very important to investigate not only the morphology of sinusitis but also the tissue metabolism in the sinus mucosa in order to reveal the mechanism which maintains the chronicity of the inflammation.

Sasaki *et al* (1959) have reported that nasal mucosa contains a proteolytic enzyme which has the action of fibrinolysis but not fibrinogenolysis, while tissues of the palate, pharyngeal tonsil etc., lack such a proteolytic enzyme. Blood has a proteolytic enzyme called plasmin, which acts on fibrin and fibrinogen by activation of the plasminogen of xynogen. From where does this proteolytic enzyme in nasal mucosa originate? Is there any relationship between this enzyme in the nasal mucosa and plasmin in blood? It will be necessary to clarify the character of the enzyme in nasal mucosa, which I termed the "nasal fibrinolytic enzyme" and then compare this with the proteolytic enzyme of other tissues. This paper deals with some observations of electrophoretic and immunoelectrophoretic studies carried out on an extract of nasal mucosa and blood serum.

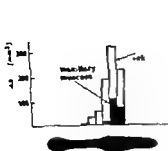


FIG. 3.

FIG. 3. Electrophoresis of the extract of the maxillary mucosa and its fibrinolytic pattern.

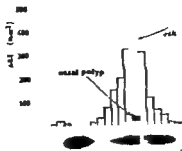


FIG. 4.

FIG. 4. Electrophoresis of the extract of the nasal polyp and its fibrinolytic pattern.

certain enzyme which induces fibrinolysis after reaction with Sh. The SK activated enzyme seemed to have a similar pattern in fibrinolysis to plasmin, which was demonstrated after the electrophoretic separation of human blood serum.

The author tried to discover whether nasal mucosa had the same protein as blood serum, using the method of immunoelectrophoresis.

The protein in nasal mucosa reacting with horse anti-whole human serum would be the same protein as human serum.

The precipitation lines forming after the reaction of the extract of nasal mucosa with antiserum are shown in Figs. 5, 6 and 7. These extracts had several precipitation lines reacting with antiserum.

Generally speaking, the nasal polyp seemed to have more precipitation lines and more types of protein than other nasal mucosa. This observation

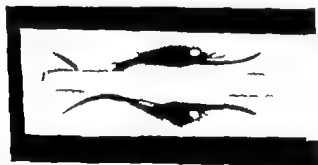


FIG. 5. Immunoelectrophoretic pattern of human blood serum (upper) and the extract of the maxillary mucosa (lower) obtained with horse anti-human serum. Amido black staining. The protein content was by the method of the Hitachi Band Prot in Refractometer. Blood serum, 7.9 g/dl; the extract of the maxillary mucosa, 4.1 g/dl.

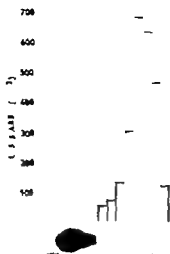


Fig. 1

FIG. 1. Electrophoresis of human blood serum and its fibrinolytic pattern after reaction with SK.

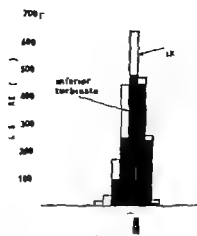


Fig. 2.

FIG. 2. Electrophoresis of the extract of the inferior turbinate and its fibrinolytic pattern.

## RESULTS

After electrophoresis of the human blood serum some sections of the agar plate brought about fibrinolysis in a fibrin plate containing SK. It was found that the proteolytic enzyme existed between the  $\alpha_2$  globulin and a part of the  $\gamma$ -globulin. The strongest activity was in the  $\beta$  globulin (Fig. 1).

The extract of the mucosa of the inferior turbinate brought about fibrinolysis in the  $\beta$  globulin and extended to a part of the  $\gamma$ -globulin. The SK-activated enzyme in this mucosa of the inferior turbinate was in the neighbouring region of the  $\alpha_2$ -globulin and extended to a part of the  $\gamma$  globulin and was a little broader than that of the mucosa of the inferior turbinate containing no SK (Fig. 2).

The extract of the maxillary sinus mucosa brought about fibrinolysis in the  $\beta$  globulin, and extended to a part of the  $\gamma$  globulin. The SK activated enzyme in the maxillary mucosa was in the  $\alpha_2$  globulin and extended to a part of the  $\gamma$  globulin. This activity was a little broader than that of the maxillary mucosa containing no SK (Fig. 3).

The nasal polyp was slightly active in the proteolysis in the  $\beta$  globulin and extended to a part of the  $\gamma$ -globulin but the SK activated enzyme was remarkably broader than that containing no SK and in some cases fibrinolysis appeared in the fraction of prealbumin (Fig. 4).

The proteolytic enzyme against fibrin in the mucosa of the inferior turbinate, maxillary mucosa and nasal polyps was most active in the fraction of the  $\beta$ -globulin region but not always parallel to the concentration of the  $\beta$  globulin.

Each nasal mucosa contains a type of fibrinolytic enzyme and also a



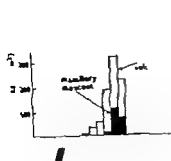


FIG. 3.

FIG. 3. Electrophoresis of the extract of the maxillary mucosa and its fibrinolytic pattern.

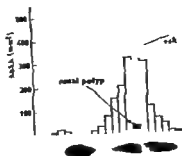


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FIG. 4. Electrophoresis of the extract of the nasal polyp and its fibrinolytic pattern.

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FIG. 5. Immunoelectrophoretic pattern of human blood serum (upper) and the extract of the maxillary mucosa (lower) obtained with horse anti-human serum. Amide black staining. The protein content was by the method of the Hatched Hand Protein Assay. Blood serum, 7.9 g/dl; the extract of the maxillary mucosa, 4.1 g/dl.



FIG. 6 Immunoelectrophoretic pattern of human serum (upper) and the extract of the inferior turbinate (lower) obtained with horse anti-human serum. Amido black staining. The protein content was by the method of the Hitachi Hand Protein Refractometer: blood serum, 7.0 g/dl the extract of the inferior turbinate, 4.6 g/dl.



FIG. 7 Immunoelectrophoretic pattern of human serum (upper) and the extract of the nasal polyp (lower) obtained with horse anti-human serum. Amido black staining. The protein content was by the method of the Hitachi Hand Protein Refractometer: blood serum, 7.9 g/dl the extract of the nasal polyp, 2.4 g/dl.

supports the previous statement that there was a broader spectrum of the SK activated enzyme in the nasal polyp compared with other nasal tissues, even though the "nasal fibrinolytic enzyme" occurs to a lesser extent in the nasal polyp than in other nasal structures.

#### DISCUSSION

The fibrinolytic enzyme in nasal mucosa appeared in the neighbouring region of the  $\beta$  globulin fraction after electrophoretic separation of the extract of nasal mucosa. This activity was not always proportional to the protein concentration of the  $\beta$ -globulin fraction and did not seem to be the same protein as the  $\beta$ -globulin. This enzyme always stayed near the original well and proved to have little electrophoretic mobility.

Many excellent investigations about plasmin, that is proteolytic enzyme in blood, have been reported during recent years. I reported a specific

fibrinolytic enzyme in nasal mucosa and in this report I comment on the character of this enzyme and plasmin by electrophoretic separation. I tried to elucidate the relationship of the nasal fibrinolytic enzyme and the SK-activated enzyme in nasal mucosa.

Miura (1965) indicated that a proactivator of plasmin is present in nasal mucosa. But nasal mucosa might take up the serum protein into its tissue through the modification of permeability in blood vessels in the inflammatory process. The severer the inflammation, for example edema or nasal polyp, the more the permeability of blood serum increases.

Immunoelectrophoretic separation showed that the extract of the nasal mucosa had several protein fractions similar to that of blood serum and this similarity was remarkable in the nasal polyp. It is worth noting that ample protein was found similar to serum in the nasal polyp which is obtained by the least contamination of blood on operation.

In the nasal polyp the SK-activated enzyme was in the fraction of the  $\gamma$ -globulin and extended to the greater part of the  $\gamma$ -globulin, which is very similar to this enzyme's behavior in blood serum.

In another report the author (1967) reported the presence of antitryptic action in the nasal polyp and its absence in the mucosa of the maxillary sinus and the inferior turbinate. This antitryptic activity was unstable against acid. Blood serum has a very high potency inhibiting trypsin activity and the majority of these antitryptic factors were destroyed by acid.

Plasminogen in blood serum converts into plasmin by activation of plasminogen by bacteriokinasin and cytolinasin. Plasmin forms a peptide such as bradykinin by breaking down protein and shows the pathological phenomenon.

These experiments indicated that some metabolic pathways in the nasal polyp are similar to blood serum. From the analytical studies of the protein constituents of these tissues, comparative study of the SK-activated enzyme in the nasal polyp and plasmin in blood serum, it was concluded that nasal polyp are under the influence of plasmin activity and other fractions in blood. Nasal mucosa had not only the nasal fibrinolytic enzyme but also the SK-activated enzyme and this SK-activated enzyme in nasal polyp appeared in the fraction of prealbumin and the greater part of the  $\gamma$ -globulin region. This might be a characteristic of nasal polyp in chronic sinusitis.

#### ZUSAMMENFASSUNG

In der Nasenschleimhaut existiert ein spezifisches proteolytisches Enzym, das als "nasales fibrinolytisches Enzym" genannt wird. Der Zusammenhang zwischen dem nasalen fibrinolytischen Enzym und einem in der Streptolysin-aktivierten Enzym in der Nase Schleimhaut oder in dem Menschenserum wird elektrophoretisch und immunoelektrophoretisch untersucht. Das nasale fibrinolytische Enzym befindet sich in der Nähe von  $\beta$ -Globulinfraction. Das SK-

aktivierte Enzym in der Nasenschleimhaut ist ebenso wie im Menschen Serum im  $\beta$ -Globulin am stärksten. Das Verbreitungsbild des SK aktivierten Enzyms im Nasenpolyp zeigt eine auffallendere Analogie zum Menschen Serum als andere Nasenschleimhautstelle. Es wird immunoelektrophoretisch bewiesen, daß das Serumweiß im Nasenpolyp mehr als im Gewebe vom anderen Nasenschleimhautteil eingenommen wird.

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## HEREDITARY PROGRESSIVE PERCEPTIVE DEAFNESS IN A FAMILY OF 72 PATIENTS

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*Of a family comprising 72 members, 12 females and 13 males were found to suffer from a hereditary progressive perceptive deafness. The inheritance is autosomal dominant, with complete penetrance. The development of the hearing loss follows a certain pattern. It involves the highest frequencies first, and at a later stage an additional low tone loss develops. Recruitment, demonstrated by the Metz recruitment test, was present in all the patients tested. Perstimulatory adaptation test (tone decay test) showed normal values in frequencies with a hearing loss less than 50 dB, but in several frequencies with a more pronounced hearing loss, there was a pathological threshold shift. The audiological results point toward a degenerative lesion in the cochlea, with a possible additional degenerative lesion in the more central structures when the hearing loss becomes more pronounced.*

Both dominant and recessive inheritance have long been recognized as causes of perceptive hearing loss and deafness. It is now generally accepted that dominant inheritance leads to a progressive hearing loss, in contrast to the recessive trait which leads to an essentially stationary hearing defect (Albrecht, 1922; Popow, 1933; Johnsen, 1932; Dolowitz & Stephens, 1961; Hulzing *et al.* 1966). Exceptions to this rule have been documented by Johnsen (1934) and by Camthorne & Hinchcliffe (1957) who have described cases with a progressive hearing loss apparently inherited in a recessive way.

Report on audiological studies of patients with a dominant hereditary progressive deafness are few and the results are to some extent controversial. Hulzing *et al.* (1966) found the hearing loss to be symmetrical, purely perceptive, affecting high frequencies first and most seriously. Plotting the mean hearing loss of the individual patient against age, they concluded that the hearing impairment proceeded most rapidly in the first three decades of life, whereafter the progression slowed down. Using a special masking method and SISI test, they found recruitment in all their patients so tested. Perstimulatory adaptation test, carried out in a frequency where the hearing loss was moderate, showed results within normal limits. In patients with a similar hearing loss Dolowitz & Stephens (1961) did not find evidence of recruitment using monaural and binaural balance test. Perstimulatory adaptation test was, with a few exceptions, normal.

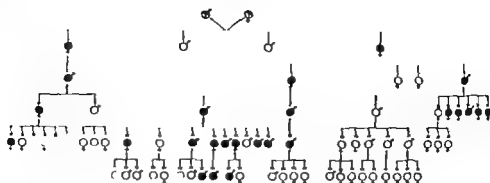


Fig. 1 Pedigree of the family examined. The inheritance is autosomal dominant with complete penetrance. ○ normal hearing, ● deaf ○ below 6 years of age ± audiometrically tested.

The present investigation of hereditary progressive perceptive deafness classifies the type of inheritance in the family examined. It describes the development pattern of the hearing loss based upon repeated registrations in the individual patient and it reports the results of recruitment tests and perstimulatory adaptation tests.

### Inheritance

The present study is of a family comprising 72 members (Fig. 1) with 25 members (12 females and 13 males) suffering from a progressive perceptive deafness. The original couple lived in Verdal, North Trøndelag. There is no information about their hearing. Two sons had normal hearing and there are no known cases of deafness among their descendants. Two daughters developed a gradual hearing loss giving difficulties in social communications at 25–30 years of age. Members of their families are well known in the area for their tendency to develop a gradual deafness from about 20 years of age.

Fifty five of the family members could still be reached in this area and all of them volunteered to a routine ENT examination and pure tone audiometry. A varying degree of perceptive hearing loss was found in 18 persons. All of them claimed to have had normal hearing during childhood and the first few years in elementary school. Following the criteria of Glorig & Nixon (1962) 35 of the examined persons were found to have a normal hearing. Two persons classified in Fig. 1 as having "normal hearing" had a sensori neural hearing loss. One who had served in the Army as artilleryist had a typical noise induced hearing loss in his right ear with a dip to 50 dB and 65 dB for the frequencies 4000 Hz and 8000 Hz respectively. The other person had a history of severe meningitis at 30 years of age followed by bilateral hearing loss, most pronounced in the lower frequencies. Seven teen persons were either deceased or had moved far away from places

where hearing tests could be done. Based on anamnestic data deafness was diagnosed in 7 of them. As seen from the family tree the inheritance is of an autosomal dominant type, with complete penetrance.

### *Audiological Results*

Many of the patients with a hearing loss had been examined in Vamdal hospital previously. For 11 persons we had audiograms registered with intervals for a period varying between 3 and 15 years. It was thus possible to follow the steady hearing deterioration in the individual patient. In all 11 patients a progression of 30 dB or more in one or more frequencies took place during the observation period.

The progression of the hearing loss follows a definite pattern. Audiograms (Fig. 2) registered with intervals in 3 patients during different age periods exemplify the general impression.

Starting in the highest frequencies before 7 years of age a hearing loss of about 60-80 dB gradually develops in frequencies above 1000 Hz. Although the low tone loss may start earlier it now proceeds to 40-60 dB for frequencies below 1000 Hz. Further development leads to complete deafness for frequencies above 1000-2000 Hz, with greatly impaired hearing acuity for the lower tones. The condition may end up with total deafness which was diagnosed in 2 of our patients. The intervals between each hearing registration have been too irregular in most of our patients to allow any conclusion as to the possibility of the existence of different stages of "relative arrestation" (Huizing *et al.*, 1966).

Twelve patients with a varying degree of hearing loss were willing to travel the long distance to the hospital for a more extensive audiological examination. Recruitment was tested, using a Madsen Impedance Meter type ZO 81. In 4 patients the eventual presence of recruitment could not be expected to be demonstrated by this method. Their hearing loss was severe with total deafness for tones over 1000-1500 Hz, and in the lower frequencies the stimulus tone could be increased very little above the hearing threshold because of the output limit of the audiometer. All 8 patients tested had recruitment. In all of them the stapedius reflex, which normally is elicited by pure tone stimuli 0-90 dB above the hearing threshold, was elicited by stimuli less than 60 dB above the hearing threshold in one or more frequencies. In several patients the reflex was elicited by stimuli with an intensity only 15-30 dB above the hearing threshold (Fig. 3).

Peristimulatory adaptation test (tone decay test) carried out in 3 or 4 frequencies in each ear was performed in all the 12 patients. The patient was presented a tone 5-10 dB above the hearing threshold and asked to hold his index finger up as long as he heard the tone. When the patient indicated that the tone disappeared, the intensity was increased in steps of 2-10 dB until he heard the tone again. This was continued until the

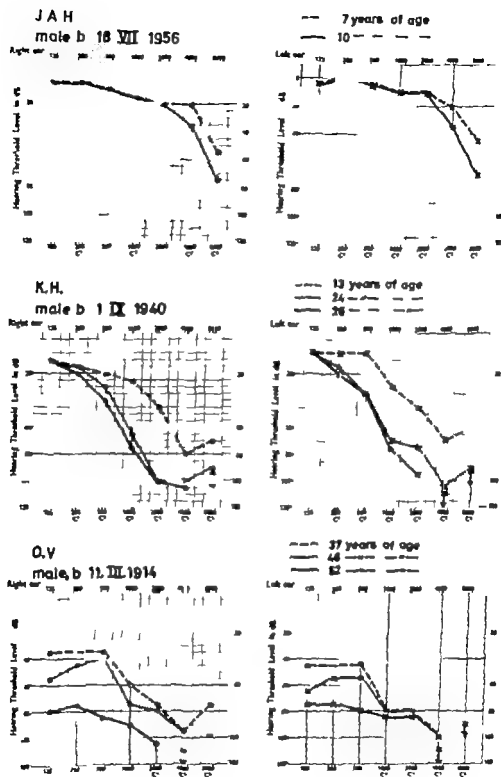


FIG. 2 Different phases of the progressive hearing loss repeated diagram in 3 patients show the progression of the hearing loss in different age periods.



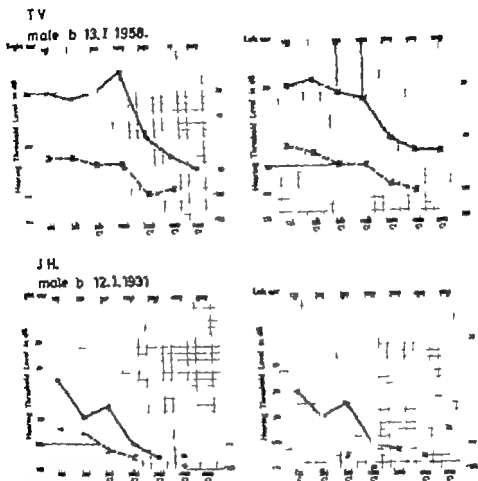


FIG. 2. Recruitment demonstrated in 2 patients by the Metz recruitment test. The Weberian mass reflex (X) is elicited by pure tone stimuli with intensity 10-15 dB above the hearing threshold.

patient could hear the tone continuously for 90 seconds, or until the maximum output of the audiometer was reached. Because of interfering tinnitus and/or lack of cooperation, the results of this tiresome and attention-demanding examination could be considered reliable in only 9 of the patients. In frequencies where the hearing loss was less than 50 dB there was no sign of pathological tone decay in any of the patients. The test was carried out in a total of 38 frequencies where the hearing loss was more than 50 dB. In 11 of these frequencies there was a threshold shift of 25 dB or more during the test. In some frequencies there was a threshold shift of 20-40 dB before the tone disappeared completely (Figs. 4a and b).

# AR female, b 18.X 1952

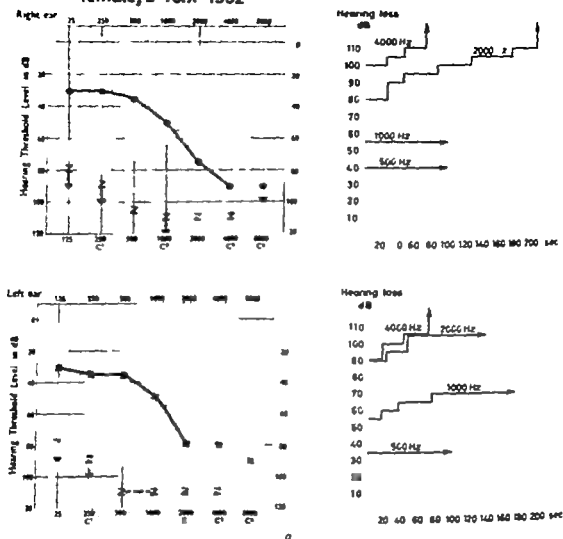


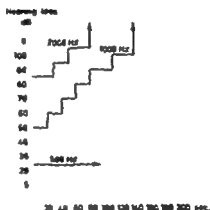
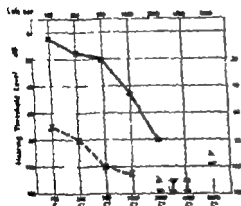
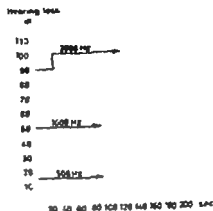
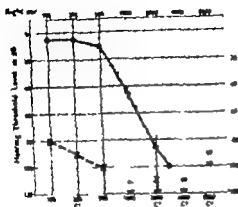
FIG. 4a d b Peristimulatory adaptation test (ton decay test) in two patients with typical hearing loss. A pathological threshold shift is demonstrated in several frequencies where the hearing loss is more than 50 dB

## DISCUSSION

The present study of progressive perceptive hearing loss caused by autosomal dominant inheritance shows that the hearing loss follows a certain pattern in its development. This pattern is the same as the one described by Dofowitz & Stephens (1961) and by Hulzing *et al.* (1966). It is therefore common not only to different members of the same family but also to different families carrying this disease.

Recruitment demonstrated by the Metz recruitment test points towards a degenerative lesion in the cochlea. Hulzing *et al.* (1966) suggested that the experimentally established existence of two systems in the cochlea (Katsuki *et al.*, 1962; Smith & Sjöstrand, 1961) one for low frequencies and one for high frequencies, might explain the separate deterioration

A.V.  
female b. 25.V.1938.



of the high and low frequency hearing in these patients. If this theory is correct an identical development of the progressive hearing loss in different affected families must be predicted. The variable results of the tone decay test in the individual patient, depending on the frequency tested, show the importance of testing several frequencies in each ear before any definite conclusion is made. The pathological tone decay found in some frequencies where the hearing loss was more than 30 dB suggests an additional degenerative lesion in the more central auditory pathways. However several authors consider an abnormal auditory adaptation a phenomenon which also can be found in cases with a lesion exclusively in the cochlea (Hood 1933).

#### ACKNOWLEDGMENTS

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# A R female, b. 18.X 1952

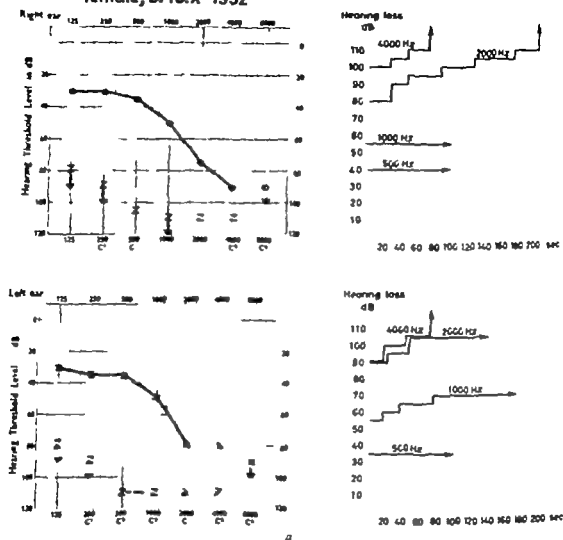


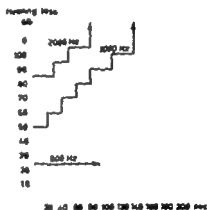
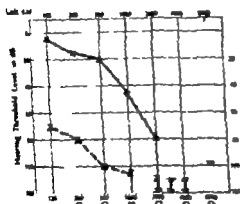
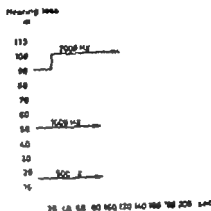
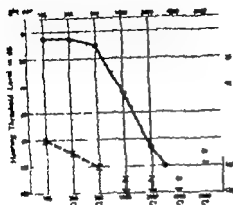
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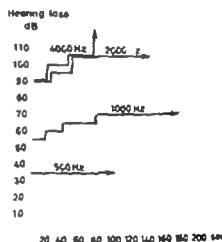
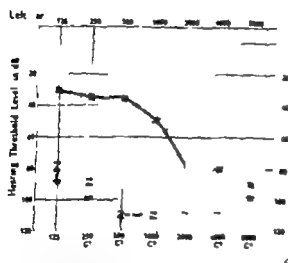
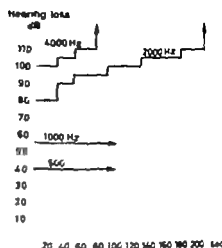
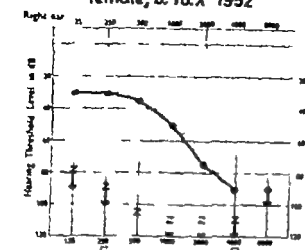


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## INFLUENCE OF CONTACT CUES ON THE PERCEPTION OF THE OCULOGRAVIC ILLUSION<sup>1</sup>

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Measurements were made on five normal and five labyrinthine-defective men when they stood erect in a room while it was stationary and again when it was rotating. The procedure was designed to produce two situations for the normal men in which otolith and nonolith information were synergistic and three others in which they were antagonistic. Perception of the visual horizontal during rotation was not systematically related to differences in head and body position nor were there significant differences between the normal and L-D men. The results show that otolith information predominates in this experimental situation.

The purpose of this study was to investigate the role of otolith and nonolith gravireceptors in the perception of the visual horizontal in darkness when observers stood on a rotating platform. It was hoped that the results would shed some light on the contribution of the nonolith gravireceptors in the perception of the visual horizontal in normal and labyrinthine-defective (L-D) men. It is well known that normal and L-D men show significant differences in such phenomena as counterrolling (Müller 1961), the oculogravic illusion (Graybiel, 1962; Graybiel & Clark 1965) and their perception of motion on a parallel swing (Guedry 1965). At the same time it is also well known that L-D men can compensate for the loss of vestibular function in certain situations. For example, Clark & Graybiel (1963) have shown that in a series of 30 successive settings to the postural vertical both normal and L-D men made systematic improvement. The normal men showed smaller average errors, but the differences were small, particularly after 15 trials, and were not statistically significant. Specifically, the present study compares the performance of normal and L-D men with various head and body positions to determine their influence on the perception of the visual horizontal.

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Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the view or endorsement of the Navy Department.

ferent family members, and to the hearing assistants at Nandol Hospital, Laila Landre R.N., and Helge Høyvik for their help with the audiological registrations.

### ZUSAMMENFASSUNG

In einer Familie bestehend aus 72 Mitgliedern hat man bei 12 Frauen und 13 Männern eine vererbliche zunehmende perzeptive Taubheit diagnostiziert. Die Vererbung ist autosomal dominant und völlig durchdringend. Die Gehörabnahme entwickelt sich nach einem speziellen Muster: es fängt im oberen Tonbereich an und betrifft später auch die tieferen Töne. Nach Verwendung der Recruitmentprobe von Metz hat man in allen Fällen die untersucht worden sind einen Lautstärkeausgleich gefunden. Die Hörermüdungsprobe (tone decay test) hat in den Tönen mit Gehörabnahme weniger als 50 dB normale Werte und in einigen Tönen mit grösserer Gehörabnahme eine pathologische Schwellenveränderung gezeigt. Die audilogische Untersuchung weist darauf hin, dass eine degenerative Schädigung der Schnecke und zusätzlich wenn die Gehörabnahme grösser ist eine mögliche Schädigung der mehr zentralen Strukturen vorliegt.

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from the horizontal axis of the device itself. The goggle was easily held in place by the observer and a flexible rubber fitting prevented light leaks under the operating conditions used. Three levels were used to monitor the alignment of the goggle apparatus, the observer's head and his body. The first level was located on the goggle itself, the second on a band over his head, and the third on his back.

### PROCEDURE

All measurements were made with observer standing with his head and body in one of five different positions with respect to gravity. After the room had been maintained at a constant velocity for one minute, the position of his head and body and the goggle were set by means of the levels. Each trial was begun by an experimenter who offset the line from the horizontal, and observer's task was merely to set it to the gravitational horizontal. Three experimenters were required for every trial. One observed the level on the observer's back to monitor his body position, a second experimenter monitored the level on the head and on the goggle and offset the luminous line before each setting, and the third made and recorded the readings. No setting was recorded unless the monitors were satisfied that the proper head and body positions were maintained within a half degree. An attempt was made to make the readings promptly in all trials because three of the positions were somewhat uncomfortable to maintain for prolonged periods. Nevertheless, observer was permitted to take as much time as he felt he needed to make an accurate setting. The light was turned off while the line was offset. The observers made five successive settings to the horizontal for each of five conditions facing forward and then five additional settings facing backward, with an interval of several hours between the two series. The five combinations of head and body position were: I. Static settings were made with observer standing on the floor with head and body erect and with the room stationary. II. Observer made settings to the visual horizontal with both head and body aligned with resultant force (RF) while he stood on the platform set at 20° and with the room rotating to produce a change of direction of RF from gravity of 20 degrees. III. This was the same as II except that the head and body were aligned with the force of gravity. IV. This was the same as II but the body was aligned with RF while the head was aligned with gravity. V. This was also the same as I except that the body was aligned with gravity while the head was aligned with RF.

### RESULTS

For the purpose of analysis, all of the data during rotation were computed as deviations from the mean of each observer's settings to gravitational horizontal under static conditions (Condition I). The mean of these

## METHOD

### *Observers*

Five normal and five deaf L-D observers were studied. The normal men were medical students who showed normal responses to caloric stimulation (McLeod & Meek, 1962) and to an ataxia test (Graybiel & Fregly, 1966). The L-D observers had acquired their bilateral deafness in childhood as a sequelae of meningitis and showed abnormal responses to the caloric and ataxia tests. All of the men had had experience in making observations in rotating devices and with the goggle device used to measure the perception of the visual horizontal.

### *Apparatus*

The experiment was conducted on the Coriolis Acceleration Platform a slow rotation room in which it is possible to rotate observers for prolonged periods. The room is a circular windowless room 20 feet in diameter and 10 feet high without central supporting members. It has a direct motor drive and the capability of controlled angular accelerations at rates up to 15 degrees per second either in a clockwise or counterclockwise direction although in this experiment it rotated only counterclockwise. Angular velocities up to 35 rpm may be maintained with an accuracy of plus or minus one per cent. It is capable of carrying a payload of about 9000 pounds, and up to ten persons may participate in an onboard experiment. It is well instrumented and has provision for a wide variety of laboratory equipment and living facilities. The operations required in this experiment were well within the limits of the device.

All of the observations were made with observer's head 7.5 feet from the center of rotation of the room and at a velocity of approximately 11.9 rpm counterclockwise. This produced a change in the direction of resultant force of 20 degrees at the observer's head. He stood facing the direction of rotation (and for a second series opposite the direction of rotation) on a platform tilted upward 20 degrees from the floor on the outboard side of the room. As a result, when he stood erect he encountered no difficulty in standing, and the resultant force acted directly from head to feet. Thus, during rotation he stood comfortably erect on the platform with his body weight slightly greater than normal.

The observer's task was to set a collimated red luminous line to the perceived horizontal. He viewed the luminous line in a self-contained apparatus mounted in a goggle which he held snugly in position before his eyes. The apparatus consisted essentially of a luminous line which was viewed by the right eye only while the left eye was in complete darkness. The luminous line could be rotated either clockwise or counterclockwise by means of a knurled knob which was easily reached by either the observer or the experimenter. The digital readout was in degrees deviation

TABLE 2. Analysis of variance summary table

Sources of variation	Sums of squares	df	Mean squares	F
Between subjects	90.9	9		
A. Normal-L.D.	8.8	1	8.8	1.00 <sup>a</sup>
Subjects within groups	62.1	8	7.8	
Within groups	361.5	10		
B. Body position	317.8	4	79.5	11.6 <sup>b</sup>
A. B.	28.1	4	7.0	1.4 <sup>b</sup>
Subjects: three groups	215.6	32	6.7	

p 0.33. p 0.01


*Perception of the Visual Horizontal during Rotation*

During rotation the mean settings to the perceived visual horizontal deviated systematically from the resultant horizontal for Conditions II to V. In each case (Table 1) this mean setting which varied from 4.0 to 8.5° was between the resultant horizontal and gravitational horizontal but much closer to the former. This means that the outboard segment of the line was set below the resultant horizontal. Specifically both the normal and the L-D observers set the luminous line clockwise from the resultant horizontal when they faced forward and counterclockwise when they faced backward. All of these deviations were statistically significant from zero (for the normals  $p < 0.001$  and for the L-Ds  $p < 0.01$  for each comparison). It should also be noted that the L-D men showed a slightly greater variance (Table 1).

An additional analysis of the significance of the difference among the various combinations of head and body position during rotation revealed that for the normal men (Table 1) there were no significant differences among Conditions II to V ( $p > 0.05$  for all comparisons). All of these settings deviated significantly from the static settings, but head and body position did not appear to be determining factors within the limits of this experiment. It should be noted in particular that the setting of the luminous line with head and body aligned with resultant force (Condition II) was no different from the setting when the head and body were aligned with the force of gravity in Condition III.

Similar results were found for the L-D men with two exceptions. There were no significant differences between Condition II and Conditions III to V nor between Condition III and IV ( $p > 0.10$  in every case). There were, however, significant differences between Condition V and Conditions II and IV ( $p < 0.01$  in each case). It should also be noted that the low mean performance of the L-D men was predominantly a result of the settings of one observer who set the line in the opposite sense from the others throughout his trials while he faced forward. It should also be noted that he had

TABLE 1

ESTIMATE OF THE GRAVITATIONAL (CONDITION I) OR GRAVITOMENTAL (OR V) HORIZONTAL, MADE BY SETTING A LUMINOUS LINE IN THE DARK						
CONDITION						
BODY POSITION						
DEVIATION FROM GRAVITY OR RESULTANT FORCE IN DEGREES	NORMAL MEN (n=11) L-D MEN (n=11)	MEAN	7	11	13	16
		S.D.	2.1	1.3	2.2	2.2
		MEAN	0.2	0.6	0.0	0.3
		S.D.	1.6	3.2	2.0	2.9

static observations was considered to be his point-of subjective-horizontal for this particular experimental situation although the deviation of the point-of subjective-horizontal from the gravitational horizontal in each case was very small (Table 1). Therefore, all of the deviations in Conditions II to V are deviations from observer's subjective horizontal using the goggle device rather than from gravity or resultant force.

An initial analysis of the data was made to determine whether the mean deviations of the settings while the observer faced forward were significantly different from those when he faced backward. Comparisons of these observations for all five conditions and for both groups of observers revealed no significant difference ( $p > 0.05$  or greater for all comparisons) between these two sets of observations. Consequently the analysis of the data (Tables 1 and 2) is made completely on the basis of the mean of the observations while observer faced forward and backward.

The combined data for the normal and L-D men and the five conditions (Table 1) were subjected to a two-way analysis of variance (Winer 1962) for repeated measures on the same elements, and the results are summarized in Table 2. The analysis revealed no significant variation between the normal and the L-D observers, but the  $F$  was significant for the five conditions. The interaction between the two conditions was not significant, indicating that the profiles for the two groups have the same shape.

### *Perception of the Visual Horizontal under Static Conditions*

When the data for the first and second series of observations (Condition I) were combined the normal men showed a mean deviation of 0.7 counterclockwise from the gravitational horizontal while the L-Ds had a mean deviation of only 0.2 clockwise. Neither of these differed significantly from zero ( $p > 0.10$  in each case). Thus, both the normals and L-Ds can be said to set the line to the gravitational horizontal with this goggle device under static conditions with a very small insignificant error.

5 Observer perceived his body as being tilted away from the horizontal floor of the room by his own effort whereas in the typical experiment on the oculogravic illusion he perceived the chair floor and his body to be tilted outboard.

6 In this study there was no pressure against the outboard side of his body as in the case of the supported, passive, apparent tilt.

The results of this experiment may be understood as a function of the complex, dynamic interaction of the many inputs from tactile receptors of the feet, kinesthetic receptors stimulated by the maintenance of bodily posture and perhaps from other proprioceptors. In Condition III for normals, otolith information and the nonotolith information from the head and trunk were the same as in the typical experiment in which the oculogravic illusion is observed. On the other hand, for both groups kinesthetic information in maintaining bodily posture was present as were tactile cues from the feet. Transient information was available from the semi-circular canals at the time observer tilted his head or body. Whereas in the situation in which the oculogravic illusion is observed there is apparent tilt of the observer, the seat, and the floor in the present experiment the information is merely that observer has tilted his body. The frame of reference for the L-D men in this experiment was, therefore, quite different with a resulting difference in the perception of the visual horizontal. It is particularly worth noting that in Condition II where their head and body were aligned with resultant force, the point-of-subjective-horizontal was also rotated with the outboard segment downward. It is suggested that this may be explained by the fact that in this ambiguous situation the outboard shoulder had a somewhat greater weight which was disparate with respect to the other information regarding the horizontal.

#### ZUSAMMENFASSUNG

Messungen wurden durchgeführt an fünf normalen und fünf labyrinth geschädigten Männern, die in einem Raum, der einmal still stand und einmal rotierte, aufrecht stand. Der Versuch war so angelegt, dass für die normalen Männer zwei Situationen geschaffen wurden, in denen Otolith- und Nicht-Otolith-Information einergütlich waren und drei andere in denen sie antagonistisch waren. Wahrnehmung der visuellen Horizontalen während der Rotation zeigte keine vermutliche Beziehung zu Unterschieden in Kopf- und Körperneigung, auch ergaben sich keine signifikanten Unterschiede zwischen normalen und L-D Männern. Die Ergebnisse zeigen dass Nicht-Otolith-Information in dieser experimentellen Anordnung vorherrscht.

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considerable difficulty maintaining the appropriate body and head positions except when he stood with head and body aligned with resultant force (Condition II)

### DISCUSSION

The results of the static observations are well known (Graybiel 1952, Graybiel & Clark 1955, Neal 1926). Both normal and L.D. men made very small errors which did not differ significantly from the gravitational horizontal. It is of interest to note that the L.D.s actually showed a smaller constant error and a smaller variance than the normals. The static data also show that observations with the goggle device produce results which are similar to those found with other devices used to determine the accuracy of the perception of the visual horizontal.

The results during rotation are clear-cut in showing no significant differences between normals and L.D. men in setting a luminous line to the horizontal under the conditions of this experiment. The data suggest that contact information from the feet and kinesthetic information from the legs and body were adequate for the L.D. observers to make the settings accurately, i.e. they were able to use the complex information available in this dynamic situation where they were required to stand erect (Jones & Vilisum 1965, Schone 1964). In the case of the normal observers, otolith information from the two head positions was integrated to produce a setting close to the resultant force. The particular role played by each sensory process is not made clear by these data. It is suggested however that kinesthetic cues are probably of special importance. This notion is supported by a study of the E-phenomenon under conditions of supported and unsupported tilt (Werner *et al.*, 1961). By interpolation from the data, it was indicated that E-phenomenon was about 3.5° for 20-degree tilts with the observer supported and that this increased to about 5.6° when he was required to maintain his own body position.

It should be emphasized that the differences between this experiment and experiments in which normal and L.D. men show differences in the perception of the visual horizontal are related to the following importances in methodology.

1. In this experiment the observer actively tilted his body from the waist and his head from the shoulders rather than being passively tilted.
2. In the present experiment the observer was not supported in any way instead of being firmly supported in position.
3. The observer's feet were firmly planted on the floor which was set at the resultant horizontal rather than sitting on a seat which was set at the gravitational horizontal.
4. In the current experiment, observer viewed a collimated luminous line of light but he was required to hold it in his hands rather than having the device supported independently.

## EFFECT OF CYANIDE ON COCHLEAR POTENTIALS

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Cochlear potentials were recorded before, during and after perfusion of the scala tympani or scala vestibuli with Ringer's solution containing 50 millimoles of sodium cyanide. Cochlear potentials, including endocochlear potential (EP) were promptly depressed by the action of cyanide and a negative potential was observed in the scala media. The intracellular resting potential within the organ of Corti was markedly decreased. Introduction of cyanide into the scala tympani was more effective than in the scala vestibuli. Spontaneous recovery of responses was observed in most of the cases. The application of anodal polarization to the cochlea enhanced cochlear microphonics (CM) which had been depressed by cyanide. These data indicate that the cochlear partition is permeable to cyanide and confirm the view that the negative potential in the anoxic scala media is essentially a depolarization potential of the hair cells in the organ of Corti.

### INTRODUCTION

Cyanide is widely utilized as a metabolic inhibitor to induce anoxia in various tissues (Lorenz de Nô, 1947; Wright, 1947; Hodgkins & Heynes, 1947; 1950; Schoepfle *et al.* 1959; Schoepfle, 1963). The most significant effect of cyanide appears to be on the cytochromes and consequently the oxygen cannot be utilized in the tissues. Cyanide blocks the transport sequence at oxidative phosphorylation stages and, reacting with the cytochromes, it prevents formation of ATP which is the principal compound supplying energy (Over, 1965). As far as the cochlear end-organ is concerned, little is known about the effect of cyanide on the cochlear potentials. Davis *et al.* (1935) reported that the cochlear potentials, including EP, were promptly abolished by small doses of sodium cyanide injected into any one of the scalae. The work reported here was undertaken in order to explore more fully the effect of cyanide on the various cochlear potentials.

### METHODS

Healthy guinea pigs anesthetized with pentobarbital sodium were used as experimental animals. When recording CM, summating potential (SP) and action potential of the auditory nerve (AP), the differential electrode

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free of  $\text{HCO}_3^-$  and  $\text{PO}_4^{3-}$  was used in an attempt to insure maximal stability of  $\text{Na}^+$  ion concentration and to prevent loss of cyanide from solution (Schoepfle *et al.* 1959). The pH and the osmolarity of this solution were 9.5 and 389 mos/kg respectively.

## RESULTS

In control experiments, the scala tympani or scala vestibuli was perfused with modified Ringer's solution which contained 107 millimoles of  $\text{Na}^+$  and the pH was adjusted to 9.5 by adding small and physiologically insignificant amounts of  $\text{NaOH}$ . EP did not show any significant changes during or after the perfusion. AP and CM did decrease their magnitude gradually during perfusion of scala tympani. With 6000 cps tone bursts of about 55 db above the just detectable threshold of CM, the depression of  $\text{V}$  was 70 to 80% and CM decreased to 85% at the end of the perfusion. Both CM and AP recovered completely within 5 minutes after completion of the perfusion. The effect of perfusion of scala vestibuli with the control perfusate was slight and complete recovery of the response was observed within 3 minutes.

The perfusion of the scala tympani with  $\text{NaCN}$  solution was carried out under the same conditions as the control. The introduction of cyanide into the scala tympani resulted in dramatic changes in cochlear potentials. First of all EP began to drop 20 to 30 seconds after the onset of the perfusion. In 13 cases the average survival time of EP defined as the time

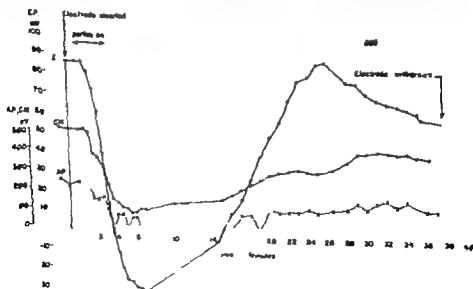


FIG. 1. Behavior of CM, AP,  $\text{V}$  and EP during and after application of 60 millimoles of  $\text{NaCN}$ -Ringer's solution to the scala tympani. Stimulus 6000 cps tone burst at approximately 55 db above the CM pseudo-threshold.

technique was employed (Tasaki *et al.*, 1952). For measurement of EP a glass pipette electrode was inserted into the scala media through the spiral ligament and connected to an electrometer. As a reference electrode a chloride-coated silver electrode was placed on intact neck muscles. The sound stimuli were tone bursts of moderate intensity between 6000 and 10 000 cps. All these techniques have been fully described elsewhere (Butler *et al.* 1960; Konishi *et al.* 1961). When recording the dc potential in the organ of Corti, a superfine capillary microelectrode was used, which was filled with 3 moles of KCl solution. Its resistance ranged from 20 to 30 megohms. The electrode tip was brought near the inner edge of the basilar membrane after removing the round window membrane and the perilymph in the scala tympani. The direction of the electrode was adjusted so as to be perpendicular to the basilar membrane. The microelectrode was then advanced toward the scala media with a hydraulic driver. The microelectrode and the reference electrode in the neck were connected to an electrometer and permanent records were obtained by delivering the output of the electrometer to an oscillograph.

The experimental method for applying the external anodal current to the hair cells was the same as that described by Tasaki *et al.* (1952) and by us (in press).

The procedure for perfusion of the perilymphatic space was essentially the same as that described in our previous paper except for a difference in its rate (Konishi *et al.* in press). A pair of small holes was made for perfusion of the scala tympani: one in the scala tympani of the basal turn and the other in the scala vestibuli of the fourth turn of the cochlea. A glass pipette containing the perfusate was inserted into a hole in the basal turn and the hole in the upper turn served as an outlet. For perfusion of the scala vestibuli a hole was made in the scala vestibuli of the basal turn to receive the perfusion pipette. The location of holes for the perfusion was carefully selected so that the perfusate could pass the area where the electrical responses were recorded. Since a distance of at least 1 mm was allowed between the perfusion pipette and recording electrodes, this length is sufficient to cover the electrical spread of ac and dc current along the cochlea (Tasaki, 1957; Konishi, unpublished data). When recording the dc potential in the organ of Corti the perfusion pipette was inserted into the scala tympani of the second turn and the round window served as an outlet as its membrane had been partially removed before the perfusion. Approximately 10 microliters of the perfusate were introduced into the perilymphatic space for 3 to 5 minutes so as to avoid mechanical displacement of the basilar membrane which is reflected by sudden changes in dc potential in the scala media. As a consequence the effective concentration of cyanide solution may be lower than the concentration actually introduced.

The perfusate used was 50 millimoles of sodium cyanide dissolved in Ringer's solution (mM NaCl 147, KCl 4.0, CaCl<sub>2</sub> 2.9). Ringer's solution

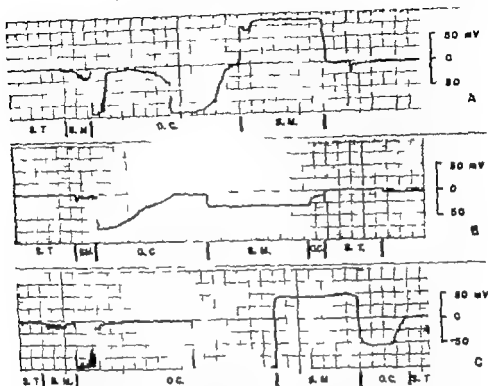


FIG. 2. Exploration of the organ of Corti with microelectrode. Reading from left to right, the trace indicates the potentials recorded as the microelectrode was moved from the scala tympani to scala media. Record A: Control before perfusion. Record B: 30 sec. after completion of perfusion of the scala tympani with 1% NaCN Ringer's solution. Record C: 1 hour after perfusion. Letters indicate location of the tip of the electrode. S.T., S.V., O.C. and S.M. represent scala tympani, basilar membrane, organ of Corti or scala media respectively.

increase in magnitude when spontaneous recovery of CM could be obtained after the perfusion. Fig. 1 illustrates one example of response changes during and after perfusion of the scala tympani with NaCN solution.

The introduction of NaCN solution into the scala vestibuli resulted in similar changes in the cochlear potentials but its effectiveness was less than that of the perfusion of the scala tympani. The average survival time of EP and CM was 9 and 13 minutes respectively in 6 cases. The maximum negative potential in the scala media after the perfusion averaged only 3 mV and ranged from 0 mV to -8 mV. Three cases showed partial recovery of CM and AP after perfusion of the scala vestibuli and recovery of EP was obtained in all 6 cases. There was little difference in the spontaneous recovery of the responses between the perfusion of the scala tympani and that of the scala vestibuli. Fig. 2 shows the response decline during and subsequent to perfusion of the scala vestibuli.

In the third series of experiments the dc potential of the organ of Corti

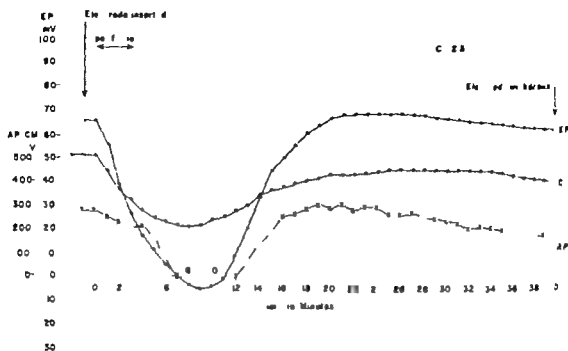


FIG. 2. An example of changes in CM, AP (V) and EP during a day after introduction of 50 millimoles of NaCN Ringer's solution into the scala vestibuli. Stimulus 6000 cps tone burst at about 55 dB above CM pseudo-threshold.

required for EP to reach zero was 4 minutes 40 seconds. Upon reaching zero EP continued to decline, thus exhibiting a negative value. This change took place when the reference electrode was placed either on the neck muscles or in the scala tympani of the basal turn. The maximum negative value ranged from  $-3$  mV to  $-35$  mV and its average was  $-20.4$  mV. The time lapse required to reach a maximum negative potential varied considerably; however, in most cases it reached its maximum within 10 minutes after the perfusion started. Both CM and AP were found to be reduced after the perfusion. With 6000 cps tone bursts of about 55 dB above the just detectable threshold of CM the average time required for CM to reach 50% of its original magnitude was about 2 minutes 30 seconds. The survival time of CM defined as the time elapsing before CM reached post mortem level ranged from 2 to 12 minutes and averaged 7 minutes 15 seconds. The survival time of  $N_1$  was shorter than that of CM and was found to average 4 minutes 30 seconds.

All our animals, except one, showed spontaneous recovery of EP after perfusion of the scala tympani with NaCN solution. EP reappeared and about one third of our cases showed a temporary supernormality. Four out of 13 cases did not show recovery of CM and AP. Both CM and AP recovered only partially in 8 cases. SP did not show consistent changes during or after the perfusion but the negative SP was increased during the initial period of the perfusion and the positive SP was often observed shortly after CM reached post mortem levels. The negative SI showed progressive

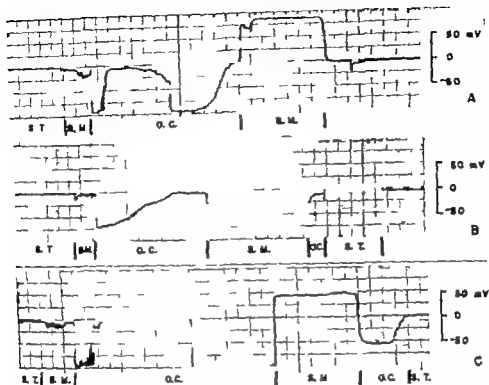


FIG. 2. Exploration of the organ of Corti with microelectrode. Reading from left to right, the trace indicates the potentials recorded as the microelectrode was moved from the scala tympani to scala media. Record A: Control before perfusion. Record B: 1 minute 30 seconds after the completion of perfusion of the scala tympani with 1% KCN in Ringer's solution. Record C: 1 hour after perfusion. Letters indicate location of the tip of the electrode. ST, BM, OC and SM represent scala tympani, basilar membrane, organ of Corti or scala media respectively.

increase in magnitude when spontaneous recovery of CM could be obtained after the perfusion. Fig. 1 illustrates one example of response changes during and after perfusion of the scala tympani with NaCN solution.

The introduction of NaCN solution into the scala vestibuli resulted in similar changes in the cochlear potentials but its effectiveness was less than that of the perfusion of the scala tympani. The average survival time of EP and CM was 9 and 13 minutes respectively in 6 cases. The maximum negative potential in the scala media after the perfusion averaged only 5 mV and ranged from 0 mV to -8 mV. Three cases showed partial recovery of CM and AP after perfusion of the scala vestibuli and recovery of EP was obtained in all 6 cases. There was little difference in the spontaneous recovery of the responses between the perfusion of the scala tympani and that of the scala vestibuli. Fig. 2 shows the response decline during and subsequent to perfusion of the scala vestibuli.

In the third series of experiments the dc potential of the organ of Corti

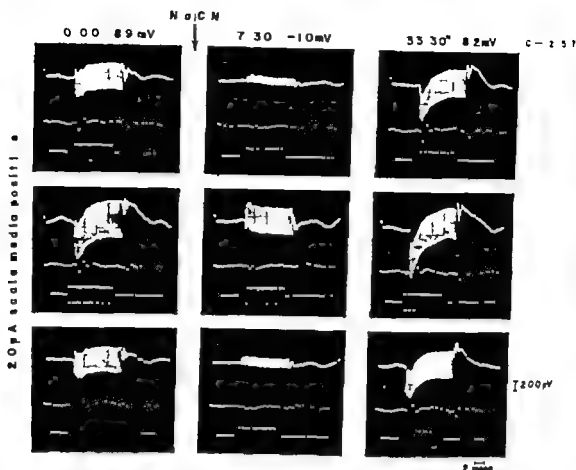


FIG. 4. Changes in cochlear potentials induced by a polarizing current flowing from scala media to scala tympani before and after introduction of  $\text{NaCN}$  into scala tympani. Numbers in the uppermost line indicate time elapsed between onset of perfusion and application of the current; those below are EP before the current was set to the cochlea. Photographs in the upper, middle, and lower rows were taken before, during, and after the application of current respectively. In each photograph, the upper tracing shows CM, the middle one AP and the bottom one stimulus. Stimulus: 9000 pps ton burst at about 50 dB above CM's audio-threshold in normal condition.

was explored with a microelectrode when the negative dc potential in the scala media reached a plateau after introduction of  $\text{NaCN}$  into the scala tympani. The exploration was carried out in rapid succession at two or three locations along the inner edge of the basilar membrane. These successive recordings almost always fell within the range of  $\pm 5$  mV. In all successful cases the resting potential in the organ of Corti ranged from  $-80$  to  $-100$  mV before perfusion. Its maximum depression after perfusion after perfusion of the scala tympani with  $\text{NaCN}$  varied considerably from  $-25$  mV to  $-70$  mV. As shown in Fig. 3 the dc resting potential in the organ of Corti was greatly depressed shortly after perfusion of the scala tympani with  $\text{NaCN}$ . This depression was reversible when the negative dc potential in the scala media recovered spontaneously after the perfusion as shown in Fig. 3.

When the scala media electrode was connected to a source of direct current and the glass pipette electrode in the scala tympani to its sink, both CM and the negative SP showed an increase in amplitude in the normal condition. When the negative dc potential in the scala media reached a maximum after the perfusion of the scala tympani with NaCN solution, the application of the dc polarization current resulted in an enormous enhancement of CM as shown in Fig. 4. The rate of this increase in CM was greater in the anoxic condition than in the normal. The changes of CM were always reversible. AP did not show any noticeable increase when the current was applied about 20 minutes after completion of the perfusion.

### DISCUSSION

There are accumulated data available showing that the cochlear potentials are highly dependent on oxygen supply (Wever *et al.*, 1949; Békésy, 1952; Davis *et al.* 1955; Glaselsson, 1955; Tonndorf *et al.* 1955; Davis, 1957; Tazaki, 1957; Fernández *et al.* 1959; Konishi *et al.*, 1961). Also it has been demonstrated that prolonged exposure of nerve to cyanide produces a gradual decline in both the action potential and the resting potential (Schmidt *et al.* 1931; Lorente de No, 1947; Wright, 1947). According to Hodgkin & Keynes (1955) NaCN inhibits active sodium extrusion which results in decrease of Na<sup>+</sup> efflux and K<sup>+</sup> influx. The inhibition of the metabolically linked sodium potassium exchange accounts for a loss of intracellular potassium. Therefore depression of the cochlear potentials by treatment with NaCN is to be expected.

The NaCN Ringer's solution was a sodium-rich hypertonic solution with a high pH. We examined the effects of these factors on cochlear potentials. Referring to these unpublished data, EP was found to endure hypertonicity and high pH of this perfusate and to be little affected by high Na concentration, although CM and AP especially AP were depressed temporarily (Konishi, unpublished data). Consequently the high pH and hypertonicity of this NaCN Ringer's solution do not seem to affect our results seriously.

The survival time of the cochlear potentials obtained in this present experiment is somewhat longer than that reported by us previously (Konishi *et al.* 1961). It is possible that this discrepancy is due to the experimental conditions. Occlusion of the anterior inferior cerebellar artery eliminates the blood flow in the cochlea promptly and completely whereas NaCN introduced into the perilymphatic space diffuses through the cochlear partition before it depresses the source of the cochlear potentials. Also the production of perilymph and leakage of the cerebrospinal fluid through the cochlear aqueduct cause dilution of NaCN Ringer's solution introduced into the perilymphatic space and this may account for spontaneous recovery of the cochlear potentials.

Among the various hypotheses put forward to explain the negative po-

tential in the anoxic scala media (Békésy 1952 Konishi *et al.*, 1961 Rice *et al.* 1961 Honrubla *et al.* 1965 Johnstone, 1965) Honrubla *et al.* postulated that the negative potential in the asphyxiated scala media is contributed by accumulation of metabolites in the scala vestibuli. If this is the case NaCN introduced into the scala vestibuli would cause a larger negative potential in the scala media than that introduced into the scala tympani. However our data demonstrate that the negative potential in the scala media is produced more effectively by the introduction of NaCN into the scala tympani. If the stria vascularis is the source of the negative potential in the anoxic scala media as one of us speculated (Konishi *et al.* 1961) then the degree of the action of NaCN on the stria vascularis would be the same regardless of which scala was perfused with NaCN.

We proposed in our previous paper (Konishi *et al.* in press) that the negative dc potential in the anoxic scala media represents an anoxic depolarization potential of the hair cells. Further evidence to support this view is the decrease of the negative potential in the organ of Corti after introduction of NaCN into the scala tympani. Butler (1965) reported that the resting potential in the organ of Corti decreased after asphyxia and he pointed out that this negative potential is of extracellular origin. The tip diameter of the glass pipette electrode used in our experiments was far less than that he used. When the resistance of the electrode changed after the penetration, indicating damage to its tip the data were discarded. Also the basilar membrane was directly visualized after careful removal of the perilymph so that the microelectrode penetrated its inner edge. Therefore we can safely assume that the negative potential recorded during the penetration of the cochlear partition is of intracellular origin. It appears from these data that the cellular elements in the organ of Corti including the hair cells, were depolarized by the action of NaCN. Similar findings were reported by Lorente de Nó (1947) that NaCN in high concentration produces a depolarization of nerve fibers in about the same manner as does oxygen lack.

The enhancement of CM by anodal polarization observed after treatment with NaCN is in line with our previous report (Konishi *et al.* in press). Schoepfle *et al.* (1959) reported that strong hyperpolarization is effective in overcoming sodium inactivation in the frog single nerve treated with NaCN Ringer's solution. Lorente de Nó (1947) also reported the ability of anodal current to increase the polarization of the membrane of anoxic nerve. Tasaki *et al.* (1952) found an increase of CM and AP when anodal current was applied to the organ of Corti and concluded that the modifications of CM and AP by anodal polarization might be due to changes in the resting potential of the cells of the organ of Corti. One possible explanation of our results is the fact that anodal polarization applied to the organ of Corti causes repolarization of the hair bearing ends of the hair cells which have been depolarized by the action of NaCN. It appears from the results in the present study that the cochlear partition is permeable to cyanide.



and that local application of cyanide causes changes in the cochlear potentials similar to those observed in other tissues (in nerve fibers, Lorente de No, 1947; Wright, 1947; Hodgkins *et al* 1955; Schoepfle, 1959 and in smooth muscle fibers, Guitman, 1959).

### CONCLUSION

A study has been made of the effect of  $\text{NaCN}$  in the perilymph on the cochlear potentials in guinea pigs.

When the perilymph was replaced with Ringer's solution containing 50 millimoles of  $\text{NaCN}$ , CM and AP were promptly depressed.

The endolymph showed a positive potential in respect to the perilymph after treatment with  $\text{NaCN}$ .

The intracellular resting potential within the organ of Corti was markedly depressed by the action of  $\text{NaCN}$ .

Cochlear potentials showed spontaneous recovery in most cases.

Application of anodal polarization enhanced CM which had been depressed by  $\text{NaCN}$ .

It is concluded from these data that the cochlear partition is permeable to  $\text{NaCN}$  and that the negative potential in the antrum (scala media) essentially a depolarization potential of the hair cells in the organ of Corti.

### ACKNOWLEDGMENT

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### ZUSAMMENFASSUNG

Cochleare Potentiale wurden registriert vor während und nach Perfusion der Scala tympani oder der Scala vestibuli mit Ringers Lösung, die 50 Millimole Natriumcyanid enthält. Cochleare Potentiale, einschließlich der endocochlearen Potentiale (EP) wurden sofort durch die Wirkung des Cyanids gehemmt und ein negatives Potential wurde in der Scala media beobachtet. Der intrazelluläre Ruhepotential innerhalb des Cortischen Organs wurde stark erniedrigt. Die Einführung von Cyanid in die Scala tympani war von größerer Wirkung als in die Scala vestibuli. Spontane Rückkehr der Reaktion wurde in den meisten Fällen beobachtet. Anodale Polarisation der Cochle verstärkte cochleare Microphonie (CM) die durch Cyanid erniedrigt worden war. Diese Resultate zeigen, dass die cochleare Trennungswand permeabel für Cyanid und bestätigen die Ansicht, dass das negative Potential in der antrischen Scala media im wesentlichen ein Depolarisations-Potential der Haarzellen des Cortischen Organs ist.

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## ISOLATED PSYCHOGENIC PALATAL MYOCLONUS AS A CAUSE OF OBJECTIVE TINNITUS

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The authors draw attention to objective tinnitus due to palatal myoclonus when occurring as a solitary complaint. The belief is expressed that in such cases psychiatric disorder is the underlying cause. The need for psychiatric treatment in these cases is stressed. Contrarily, palatal myoclonus as a component of neurological syndromes is attributed to organic lesions of the central nervous system. These conclusions are based on five illustrative cases and a review of the literature. Any classification of the tinnitus has to be extended to include subdivisions of palatal myoclonus into psychogenic and organic varieties as distinct categories.

Objective (vibratory) tinnitus is, relatively, a rare condition and represents only a small proportion of cases suffering from noise in the ears. In spite of its rarity this is a well known entity in which the sound heard by the patient can, under certain conditions, also be perceived by the examiner (Pulec & Simonson, 1961; Graham, 1965; Wengraf, 1967). The diagnosis is simple and is made either by auscultation with a stethoscope, or by listening through an auditory tube connecting the patient's and the examiner's ears. Recording of the objective tinnitus is possible using a phonocardiograph, as described by Engström & Graf (1950, 1952) and Wengraf (1967).

Etiologically the objective tinnitus is divided into two distinct groups. First, apparently the minority group where the noise is due to vascular pathology (Engström & Graf 1950, 1952; Bonnal & Legré 1960; Wengraf 1967). The second, larger group where the tinnitus is caused by clonus of the palatal and pharyngeal muscles. Several different causes of myoclonus of palate have been described (Björk, 1954; Pulec & Simonson, 1961; Wengraf, 1967).

In this paper we present five cases, where objective tinnitus due to myoclonus appeared as the only complaint. In all of them, psychogenic disorders were firmly found to be the underlying cause.

It is our purpose to propose that when palatal myoclonus appears as the solitary symptom, it is always of psychogenic origin.

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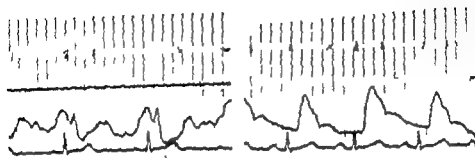


Fig. 1

Fig. 2

FIG. 1. Phonographic recording of objective titillation due to palatal myoclonus. The upper tracing represents phonocardiogram. The beat-to-beat recording of the right jugular neck pressure. At the bottom, EKG recording. No relationship with any manifestation of cardiac activity.

FIG. 2. Four tracings showing intensity of palatal myoclonus during basal condition.

### Case 3

A 37-year-old married female, mother of 3 children presented herself with complaints of a rhythmic, incessant noise in her left nostril and left maxillary area. The noise could be heard clearly at a distance of approximately one meter. This cephalic murmur was heard with a stethoscope over the left maxilla, but could be heard neither in the ear nor over the mastoid. Myoclonus of the soft palate was clearly seen both with the mouth open and through the nose. The psychiatric investigation revealed that in addition to the appearance of tinnitus, the patient offered multiple complaints, mainly in the genital and urological systems. At the conclusion of the psychiatric investigation compulsive neurosis with conversive reactions was diagnosed. As in other cases, the tinnitus was regarded as a somatic expression.

### Case 4

An 18-year-old male appeared because of a disturbing clicking tinnitus in both ears, which was greater in the right side. On examination eardrums appeared normal and audiometry revealed perfect hearing. The radiography revealed normal temporal bones.

The clicking sound in both ears could be heard with the aid of the auditory tube which was louder on the right side. The sound was not synchronous with the pulse and did not change its character with head movements. It could be stopped when the patient opened his mouth widely but on slight opening palatal myoclonus was observed. Neurological examination did not reveal deviations from the norm.

According to psychiatric examination the patient faced a severe conflict

## *Case Reports*

### *Case 1*

A 27 year-old married male First examined in our outpatient clinic seven years after the onset of tinnitus in his left ear The history revealed that during those years he was examined by several physicians and hospitalized in different medical institutions. None of the treatments he underwent stopped or even changed the nature of the sound The otoscopic findings were normal as well as the audiogram and X rays of temporal bones

The patient's claim that the sound could be heard by the examiner proved to be correct. When connected to patient's ear a clicking regular sound not synchronised with the pulse, was heard The bruit could not be heard on auscultation over the mastoid and was influenced neither by head movements nor by pressure on the carotid artery The sound could be stopped temporarily by wide opening of the mouth and could change its character and become bilateral in a Valsalva maneuver The sound and its bilatinality in a Valsalva maneuver were well demonstrated on recording with the phonocardiograph (Figs. 1 and 2)

Repeated investigations revealed rhythmic contractions of the soft palate corresponding to myoclonus.

The patient's behaviour and personality were suggestive of psychogenic disorders He was referred for a psychiatric evaluation which established—beyond any doubt—schizophrenia with an obvious paranoid pattern The myoclonus was interpreted as a somatisation of a compulsive defence mechanism We were advised against any mechanic therapeutic attempts to eliminate the tinnitus, so as not to precipitate an aggravation of his psychiatric disorder He remained under psychiatric care

### *Case 2*

A 63 year-old man was seen in the ENT clinic because of a troublesome clicking sound in his left ear which appeared three years prior to the examination The eardrums, as well as the other ENT organs, were normal The audiometry revealed bilateral equal high tone hearing loss of about 35 dB interpreted as presbycusis A clicking rhythmic sound could be heard when connected with patient's left ear It could be stopped voluntarily but reappeared spontaneously shortly thereafter When myoclonus of the soft palate was found the patient was referred for psychiatric evaluation The investigation revealed that the onset of the tinnitus coincided with a severe traumatic experience (sudden death of several members of his family) which caused loneliness, retirement and general depression. It was concluded that the myoclonus represented a compulsive tic due to tension and depression He remained under psychiatric care

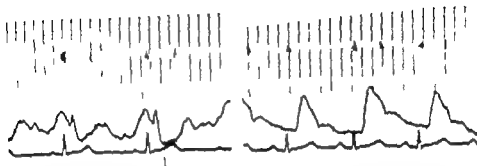


FIG. 1

FIG. 2.

FIG. 1 Phonographic recording of objective tinnitus due to palatal myoclonus. The upper tracing represents phonocardiogram. The next one, recording of the tinnitus. Below jugular venous pressure. At the bottom, EKG recording. No relationship with any manifestation of cardiac activity.

FIG. 2 Four tracings above. Baseline of palatal myoclonus during Valsalva maneuver.

### Case 3

A 37-year-old married female, mother of 3 children, presented herself with complaints of a rhythmic, incessant noise in her left nostril and left maxillary area. The noise could be heard clearly at a distance of approximately one meter. This cephalic murmur was heard with a stethoscope over the left maxilla but could be heard neither in the ear nor over the mastoid. Myoclonus of the soft palate was clearly seen both with the mouth open and through the nose. The psychiatric investigation revealed that in addition to the appearance of tinnitus, the patient offered multiple complaints, mainly in the genital and urological systems. At the conclusion of the psychiatric investigation compulsive neurosis with convergent reactions was diagnosed. As in other cases, the tinnitus was regarded as a somatic expression.

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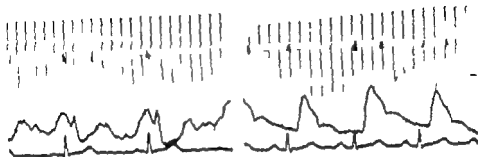


FIG. 1

FIG. 2

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FIG. 2 Few tracings as above. Synchronicity of palatal myoclonus during Valsalva maneuver.

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A 37-year-old married female, mother of 3 children, presented herself with complaints of a rhythmic, incessant noise in her left nostril and left maxillary area. The noise could be heard clearly at a distance of approximately one meter. This cephalic murmur was heard with a stethoscope over the left maxilla, but could be heard neither in the ear nor over the mastoid. Myoclonus of the soft palate was clearly seen both with the mouth open and through the nose. The psychiatric investigation revealed that in addition to the appearance of tinnitus, the patient offered multiple complaints, mainly in the genital and urological systems. At the conclusion of the psychiatric investigation compulsive neurosis with convergent reactions was diagnosed. As in other cases, the tinnitus was regarded as a somatic expression.

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According to psychiatric examination the patient faced a severe conflict

with his father and the palatal myoclonus represented a neurotic reaction as a flight into disease. He was advised to receive psychiatric treatment.

### Case 5

A 19-year-old female presented herself in the outpatient department with a complaint of a noise in the head of more than a year's duration. The onset of this complaint coincided with her father's sudden death. The father himself had suffered from facial tic and chronic coryza. This 'cephalic murmur' could be heard from a distance of about one meter. It had a clicking character, not synchronous with the pulse. Palatal myoclonus was clearly seen, the contractions being synchronous with the clicking sound.

There was nothing abnormal discovered on E.A.T. examination; hearing was normal as well as X rays of sinuses and mastoids.

A psychiatric examination revealed an anxiety neurosis with conversion symptoms, aggravated by the death of the father. The patient was referred for further psychiatric treatment.

### DISCUSSION

The differential diagnosis between the objective tinnitus of vascular origin and that due to palatal myoclonus is based mainly on the character of the noise. In the first type the sound is murmur-like, synchronous with the heart beat and it may change when the carotid artery is compressed. In palatal myoclonus, on the other hand, there is a characteristic click which bears no relation to the pulse. Its quality may be altered by activating the pharyngeal muscles. The differences between these two groups may be clearly demonstrated by means of phonography (Figs. 1 and 3).

The cause of palatal myoclonus has been attributed to various lesions, among them vascular pathology, multiple sclerosis, aneurysm or vertebral artery, different tumors involving the brain stem or cerebellum and apoplexy (Bjork 1954; Parker 1956; Pulce & Simonton 1961). On the other hand, non-organic disturbances, such as emotional conflicts, neurasthenia and neurosis have also been incriminated (Bjork 1954; Pulce & Simonton 1961).

Palatal myoclonus has been described in association with different neurological symptoms, such as hemiplegia, nystagmus, facial paralysis, incoordination of movements, diplopia etc. (Nathanson 1956). Even though it played only a minor rôle within much larger neurological syndromes, it has been noted for its persistency. The click in these cases was heard uninterruptedly even in sleep, anesthesia and in terminal coma.

As stated by Nathanson (1956), some of these reported cases were examined post mortem and it was found that the primary pathology was located in the cerebellar hemisphere and was associated with secondary retrograde changes in the opposite inferior olive. Myoclonic retraction of

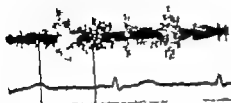


FIG. 3.

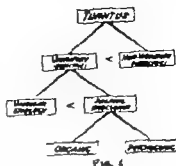


FIG. 4.

FIG. 3. Photographic recording of objective titillation of sacular origin, & those case  
 FIG. 4. Diagrammatic representation of classification of tics.

the palate has been experimentally produced in monkeys by electric stimulation in the region of the inferior olive (Weinstein & Bender 1943).

These observations warrant the conclusion that when myoclonus of the palate appears within broader neurological complex, it is caused by an organic disease. Palatal myoclonus, when it appears as a solitary symptom, is of entirely different character. In all our cases, the patients were able to control it to a certain degree. In most instances it could be interrupted by opening of the mouth. The disease did not progress (in contrast to the evolutive character in the former group) and no additional symptoms appeared, even though the condition was in the majority of cases of long duration. This point has been demonstrated also by other authors (Björk, 1954; Pulec & Simonton 1961). Heller (1962) cites a case of more than 20 years duration.

In all our cases, an underlying psychiatric disease was firmly established. The myoclonus was attributed to a tic, although the psychiatric entities were different (schizophrenia, depressive state, conversion reaction, anxiety neurosis, etc.). In some cases an emotional trauma triggered the appearance of the tic (in two instances death of relatives). Furthermore on reviewing the literature it was noted that all cases reported as solitary myoclonus had an underlying emotional disturbance and most of them were described as a tic (Schwartz, 1948; Björk, 1954; Pulec & Simonton, 1961; Heller 1962).

### CONCLUSION

In view of these considerations it may be concluded that, whereas myoclonus participating in neurological syndrome is of organic origin, when it appears as a solitary phenomenon, it is always of psychogenic nature. In these cases it is mandatory to refer the patient for psychiatric evaluation and treatment. Mechanical interference with the tic should be undertaken, so as not to disturb the patient's delicate emotional balance and precipitate a deterioration of psychiatric condition.

The place of psychogenic myoclonus in the wider constellation of tinnitus of all types is indicated by the classification offered (Fig 4)

### ACKNOWLEDGMENTS

The authors express their gratitude to Dr S Kulcsar Head of Psychiatric department for his guidance and instruction in evaluation of the psychiatric aspects. We are greatly indebted to Dr J Kraus, senior cardiologist, Heart Institute, Tel Hashomer Hospital for his contribution in performing and interpreting phonographic recordings

### ZUSAMMENFASSUNG

Die Autoren besprechen in dieser Arbeit den objektiven Tinnitus, der durch Myoclonus des weichen Gaumens hervorgerufen wird, wenn dieser als Einzelsymptom besteht. Es wird angenommen, dass eine psychiatrische Störung der ätiologische Faktor ist. Die Notwendigkeit einer psychiatrischen Behandlung wird betont. Andererseits ist der Myoclonus des weichen Gaumens als Komponente neurologischer Syndrome mit organischen Läsionen des ZNS verbunden. Fünf Fälle dienen als illustrative Beispiele der hier angeführten Zusammenhänge. Die Besprechung der einschlägigen Literatur wird in diesem Sinne interpretiert. Die Autoren schlagen eine Unterteilung des Myoclonus des weichen Gaumens in eine psychogene oder organische Form als unterschiedliche Kategorien vor.

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## OLFACTORY ESTHESIONEUROMA

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A case of olfactory esthesioneuroma is reported with special reference to the histogenesis of this unusual nasal tumor. The urinary excretion of 3-methoxy- $\gamma$ -*l*-hydroxymandellic acid was found to be well within the range of normality and this is regarded as additional, if indirect, evidence for the view that the tumor is of olfactory epithelial origin.

Olfactory esthesioneuroma is an unusual neurogenic tumor of the nasal fossa. Berger *et al.* reported the first case in 1924 and called it "esthésioneuroépithéliome olfactif" and considered the olfactory mucosa the site of origin. Two years later Berger & Coulaud (1926) described a histologically slightly different tumor and termed it "esthésioneurocytome olfactif". They proposed "olfactory esthesioneuroma" as a generic term which would include different histological subtypes. This term has been used by a few authors, but the designation "olfactory esthesioneuroblastoma" is more common. Unfortunately this last term is also used in microscopical classification.

Only about 100 cases have been reported in the literature, but the tumor is probably not quite so rare as McCormack & Harris (1935) reported 3 cases out of 80 nasal tumors and Oberl *et al.* (1960) found 8 cases in a systematic retrospective study of 504 selected cases of intranasal neoplasms.

### *Case Report*

The patient, a woman 68 years old, was first seen in October 1966. The symptoms were constant, left nasal obstruction, nasal discharge and prominence of the left eye of 6 weeks duration. In addition, she had suffered from intermittent nasal obstruction and slight frontal headaches 6 months previously. Since 1955 a hypertension had been known and treated.

On examination a grey easily bleeding tumor was seen, filling the whole left nasal fossa. No tumor was found in the nasopharynx. The left eye was protruding with limitation of eye movement and on pressure a retrobulbar resistance was felt. Sinus roentgenograms, including tomograms, revealed a soft tissue density of the left nasal cavity, clouding of the left-sided sinuses and destruction of the orbital and cribriform plate of the ethmoid bone. No cervical or pulmonary metastases were found. The urine was analysed for 3-methoxy- $\gamma$ -*l*-hydroxymandellic acid (VMA) and was found to

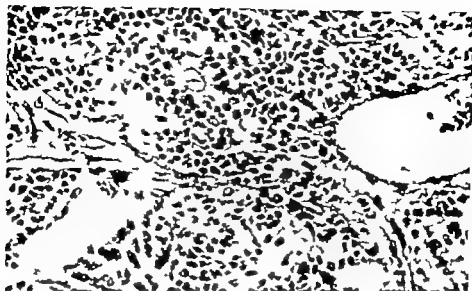


Fig. 1 Olfactory esthesioneuroepithelioma. Hematoxylin-eosin.  $\times 300$

contain 3.5 mg VMA/24 hours compared with the normal value 2-8 mg/24 hours. ESR 10 mm/hour and the blood pressure 225/120

Histological examination of biopsy specimen was performed by J V Thorborg MD. The tumor was covered by a layer of loose connective tissue which extended into the tumor dividing it into compact cell groups. The majority of the tumor cells were small with sparse cytoplasm and polymorphous nuclei (Fig 1). There were numerous mitotic figures. In all parts of the cellular tumor tissue there were typical true rosettes, formed by more or less cylindrical cells around a central lumen containing a homogenous or granular substance (Fig 2). This substance and parts of a few of the marginal cells were PAS positive and also stained by Alcian Blue. There were transitional forms between the small anaplastic and the epithelial cells. Silver impregnation (Bielschowsky) demonstrated the existence of fibrils, mostly in the stroma; no connection between these fibrils and the cytoplasm of the tumor cells could be seen. The tumor was highly vascular and a few tumor emboli were visible in the thin walled blood vessels. Diagnosis: Olfactory esthesioneuroepithelioma.

The tumor was considered inoperable and the patient was transferred to the Radium Centre Aarhus where she was treated with cobalt 60 teletherapy. On completion of therapy no gross mass was visible in the nose but there was still a retrobulbar resistance, which had decreased by April 1967 when the patient was last examined.

#### *Pathology of Olfactory Esthesioneuroma*

Macroscopically the tumor usually is a polypoid grey red easily bleeding lesion located high in the nasal fossa but the gross appearance varies, and

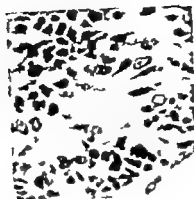


FIG. 11 Olfactory esthesioneuroepithelioma, true rosette. Hematoxylin-eosin. 400.

the diagnosis is based on microscopical examination. Histologically the tumor is subdivided according to the presence or absence of rosettes. The *esthesioneuroepithelioma* is composed of epithelial as well as neural elements. Some of the tumor cells are cylindrical and grouped around a central cavity forming true rosettes, the so-called "rosettes pseudoglandulaires." The lumen is empty or contains an amorphous substance—often periodic acid-Schiff positive as in the present case—interpreted as cellular debris, and not as a true secretion product. The neural elements are fibrils and small lymphocytoid tumor cells (esthesioneurocytes) arranged in compact groups. In the *esthesioneurocytoma* the tumor cells are esthesioneurocytes and there are no true rosettes. A third type characterized by pseudorosettes (a circle of cells around a central area containing fibrils) has been described as the *esthesioneuroblastoma*. This type is ill-defined. The cells of the pseudorosettes do not differ from the other tumor cells, as in true rosettes, and it is often a question of interpretation how to define pseudorosettes. McCormack & Harris (1935) found no pseudorosettes in metastases from an esthesioneuroblastoma, although metastases otherwise are considered identical to the primary tumor (Gerard Marchant & Mérieux, 1965). The last two types lack epithelial differentiation and contain only neural elements, and some authors (e.g. Mendeloff 1957) prefer to consider these types as one group. Other authors (Becker & Jacob, 1964; Rahne 1965) have found no reason for making subdivisions.

Errors in microscopical diagnosis are common. The tumor is often diagnosed as an anaplastic carcinoma or a lymphosarcoma, but has also to be distinguished from other small-cell neoplasms. Oberl *et al* (1960) considered the presence of fibrils essential in the diagnosis, but fibrils are not always possible to demonstrate (Mendeloff 1957; Hutter *et al* 1963). The olfactory esthesioneuroma possesses further some points of resemblance to the retinoblastoma and the sympathicoblastoma.

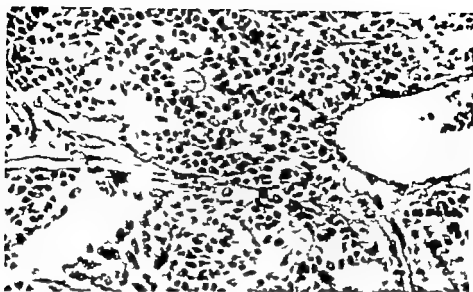


FIG 1 Olfactory esthesion uroepithelioma Hematoxylin-eosin  $\times 300$

contain 3.5 mg VMA/24 hours compared with the normal value 2-8 mg/24 hours. ESR 10 mm/hour and the blood pressure 225/120

Histological examination of biopsy specimen was performed by J V Thorborg MD. The tumor was covered by a layer of loose connective tissue which extended into the tumor dividing it into compact cell groups. The majority of the tumor cells were small with sparse cytoplasm and polymorphous nuclei (Fig 1). There were numerous mitotic figures. In all parts of the cellular tumor tissue there were typical true rosettes, formed by more or less cylindrical cells around a central lumen containing a homogenous or granular substance (Fig 2). This substance and parts of a few of the marginal cells were PAS positive and also stained by Alcian Blue. There were transitional forms between the small anaplastic and the epithelial cells. Silver impregnation (Bielschowsky) demonstrated the existence of fibrils, mostly in the stroma. No connection between these fibrils and the cytoplasm of the tumor cells could be seen. The tumor was highly vascular and a few tumor emboli were visible in the thin walled blood vessels. **Diagnosis:** Olfactory esthesioneuroepithelioma.

The tumor was considered inoperable and the patient was transferred to the Radium Centre, Aarhus where she was treated with cobalt 60 teletherapy. On completion of therapy no gross mass was visible in the nose, but there was still a retrobulbar resistance which had decreased by April 1967 when the patient was last examined.

#### *Pathology of Olfactory Esthesioneuroma*

Macroscopically the tumor usually is a polypoid grey red easily bleeding lesion located high in the nasal fossa, but the gross appearance varies and



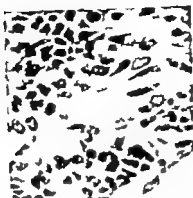


FIG. 2. Olfactory esthesioneuroepithelioma, true rosette. Hematoxylin-eosin. 600.

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Errors in microscopical diagnosis are common. The tumor is often diagnosed as an anaplastic carcinoma or a lymphosarcoma, but has also to be distinguished from other small-cell neoplasms. Obert *et al.* (1960) considered the presence of fibrils essential in the diagnosis, but fibrils are not always possible to demonstrate (Mendeloff 1937; Hutter *et al.* 1963). The olfactory esthesioneuroma possesses further some points of resemblance to the retinoblastoma and the sympatheticoblastoma.

### Theories of Histogenesis

It is generally accepted that the tumor arises independently of the central nervous system. The olfactory epithelium probably is the site of origin as almost all olfactory esthesioneuromas originate from the upper part of the nasal cavity (Obert *et al.*, 1960) and the histological picture of epithelial and neural components points in the same direction. The rosettes are supposed to be derived from the supporting cells and the esthesioneurocytes from the nerve cells of the olfactory epithelium. A few esthesioneuromas are located in the maxillary sinus or the nasopharynx (Piquet 1950, Church & Uhler 1959, King, 1959, Mashberg *et al.* 1960) and may possibly have been developed from displaced cells of the ectodermal olfactory placodes during the embryonic stage.

A few cases of this tumor have been published as sympathicoblastomas on account of the similarity of microscopical features, and Escat (1931) considered the sphenopalatine ganglion as the origin, but if so, most esthesioneuromas should be localized in the nasopharynx. Besides, there is an important clinical difference between sympathicoblastoma and olfactory esthesioneuroma as the former tumor is highly malignant and occurs almost exclusively in infancy and early childhood whereas the latter is a relatively benign lesion of the adult. The urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA) which is the chief breakdown product of catecholamines, is often increased in cases of tumors of the sympathetic nervous tissue. In the present case the urinary excretion of VMA was found to lie within the normal range. The fact of VMA being normal could be taken as support for the view that the tumor is one of olfactory epithelial origin. The blood pressure was elevated, probably due to essential hypertension and not because of production of catecholamines in the tumor. Normal blood pressure is mentioned by some authors (Frühling & Wild, 1964, Mashberg *et al.*, 1960).

Other suggested origins are the organ of Jacobson and the ganglion Loci of the terminal nerve but these are not consistent with the usual localization of the olfactory esthesioneuromas.

### Symptomatology

The olfactory esthesioneuroma occurs predominantly in adults, with the greatest frequency in the age group ten to forty years. The youngest reported patient was a child nine years old and the oldest seventy nine. No great differential sex incidence has been established. The symptoms, which are non specific, begin with unilateral nasal obstruction, frequent epistaxis and nasal discharge less often with excessive lacrimation or anosmia. When the tumor becomes locally invasive there may be unilateral exophthalmos, diplopia, swelling of the root of the nose or headaches. Sinusitis, following blocking of the natural ostia, may cause the headache. The

neoplasm may grow through the cribriform plate with secondary invasion of the brain, not necessarily giving cerebral symptoms. The tumor is usually slow growing and metastases occur only in 20 per cent of the cases, first in the cervical lymphnodes later in lungs, bones, and seldom in the spinal cord through the cerebrospinal fluid (Hlemenschneider & Prior 1958). Roentgenologic examinations are of value in estimating the extension of the tumor. Tingwald (1966) used mercury 203 scintigrams in the diagnosis of brain metastases.

### Treatment and Prognosis

The tumor is usually radiosensitive and irradiation ought to be part of the treatment. Some authors consider the esthesioneurocytoma less radio-sensitive than the esthesioneuroepithelioma which was also observed by Berger *et al* in the two cases. At present this distinction is not sufficiently confirmed. A few cases were radioresistant (Becker & Jacob, 1964; Ellis-Hugh *et al* 1966; Grahne, 1966). Radical surgery may be undertaken, but is often impossible. Experience with cytostatic therapy is scarce (Mendel 1957; Becker & Jacob, 1964; Grahne, 1966; Tingwald, 1966) but this treatment has been of some palliative value. At present the treatment to be preferred seems to be local excision, followed by radiation therapy.

Skolnik *et al* (1966) found 50 patients in the literature followed up for more than 11 years. The five years survival was 42 per cent. Through treatments with surgery, irradiation and combined therapy the five years survival percentage was 64, 38, and 30, respectively values which probably reflect the effect of the tumor extension on the choice of treatment. Some authors (McCormack & Harris, 1963; Gerard-Marchant & Michenu, 1963) found a relationship between the histological picture and the prognosis, but no consistent relationship has as yet been convincingly established.

### ZUSAMMENFASSUNG

Ein Fall von seltenem Nasentumor Esthesioneurom des Olfactorium, wird beschrieben, mit besonderem Hinblick auf die Histogenese. Die Ausscheidung im Urin von 3-Methoxy-4-Hydroxy-Mandelsäure ist normal geblieben was die Aufklärung der Riechschleimhaut als Entstehungsort des Tumors unterstützt.

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## HYALINOSIS CUTIS ET VILCOSAE (LIPOID PROTEINOSIS)

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The features of lipoid proteinosis in which are of particular interest to the laryngologist are reviewed. It is suggested that raised serum alkaline phosphatase of the case described could be the result of increased lipoglycoprotein synthesis and that a long term consequence of this is endocranial calcification. The latter has been clearly localized. It is also suggested that in a family in which lipoid proteinosis occurs in one member the raised serum alkaline phosphatase may perhaps be taken as an indication of latent lipoid proteinosis in an otherwise clinically normal member.

The rarity with which the very interesting disorder of lipoid proteinosis is found in this country is clear from the fact that the first known British case was reported only in 1961 by Cowan *et al*. Urbach & Wiethe have been credited with the first description of this condition in 1929 after a very comprehensive study though the very first case of lipoid proteinosis was probably recorded by the laryngologist Siebenmann in 1908. Commonly the earliest symptom is inability to cry or make any of the normal vocal sounds of infancy followed by increasing hoarseness as the child grows older.

The changes in the upper respiratory tract are quite striking, and lesions of the oropharynx itself are often pathognomonic. The buccal surface of the lips are thickened with yellowish or white deposits in the mucosa, which have either a fine granular appearance or else coalesce into diffuse plaques (Caplan, 1962; Cowan *et al*, 1961; Lower, 1948). These may extend to the cutaneous margin, as they do at other mucocutaneous junctions and the lips become thickened and rather doughy in consistency. Fissuring may occur at the angles of the mouth (Fine *et al*, 1962; Raymond Jones, 1963).

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of the tongue to the dental margin. The tongue itself is firmer than usual and can be almost woody hard (Caplan 1962, Dickey & Davis, 1964).

The anterior nares, like the lips, lose their normal softness and capacity to widen by the dilator nares and may become narrowed. The nasal mucosa is less commonly affected, though there can be an associated atrophic rhinitis (Cowan *et al* 1961). However a similar mucosal change can extend from the post nasal space over the posterior pharyngeal wall to the laryngo-pharynx. The thickening and reduced mobility of the pharyngeal wall associated with this may lead to some dysphagia and this sensation is occasionally made worse by a grossly thickened epiglottis (Lower 1948, Raymond Jones, 1965).

The aryepiglottic folds stand out as white, thickened uneven, glistening or granular bands and the process extends down on to the mucosa of the arytenoids, causing some limitation of movement of the crico-arytenoid joint. Both the false and true vocal cords are similarly affected, the latter often having a rather nodular margin, thus increasing the huskiness of the voice (Caplan 1962, Cowan *et al* 1961, Dickey 1964, Scott & Findlay 1960).

However the process need not necessarily involve all the upper respiratory tract and while one part may be grossly involved, another may be clinically quite clear. Though the prognosis on the whole is good in these cases, the most common danger to life is one of upper respiratory obstruction and of the 14 cases reported by Urbach & Wiethe, 1929, no less than 8 eventually required tracheostomy.

Having pointed out those aspects of lipoid proteinosis which are of particular interest to the laryngologist, the following case of a boy, aged 18 years, presents a varied pathology and is of general interest. It is particularly interesting because of the precise localisation of the intracranial calcification present, the long follow up of his laryngeal changes, and also the abnormal bio-chemistry of himself and of his sister, who was otherwise clinically normal.

### *Case Report*

A schoolboy, then 15 years old, was first seen at the Royal Infirmary, Manchester, in November 1962. He had spoken in a whisper from birth and had been husky ever since. He had always had to drink lukewarm rather than hot fluids and could never put his tongue out even from an early age. Some small warty outgrowths had developed on his knees at the age of 8 years and these had been removed by a local cautery. They had recurred at the age of 11 years and at that time he also developed warty hyperkeratotic plaques on the elbows. The skin of the back of his hands and of his axillae was rather fixed and waxy and there was loss of the normal contours of both pinnae. Small pearly bead like lesions had studded his eyelids from the age of 11 years (Fig. 1).

There was no family history of skin disease or of hoarseness, nor was

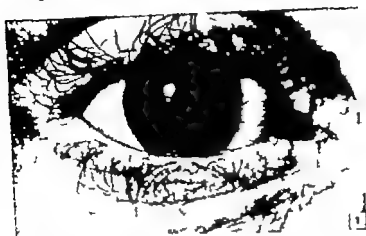


FIG. 1 Pearly lead-like lesions surrounding the eyelids.

there any consanguinity. Clinical examination of the father aged 40, the mother aged 44 and the sister aged 9, including their upper respiratory tract, was normal.

In August 1950 at the age of 2, a direct laryngoscopy had shown a small cyst of the posterior third of the left aryepiglottic fold and this was removed. A further direct laryngoscopy in October 1951 revealed another cyst in the same position. An attempt was made to remove this cyst but the material collapsed and no biopsy specimen could be obtained. He was kept under repeated observation and in May 1954 direct laryngoscopy showed a general thickening of all parts of the upper aperture of the larynx. No further cyst was present. A web was reported anterior to both arytenoid areas in September 1955, and in November 1956, direct laryngoscopy under light anaesthesia showed that the movements of both vocal cords were within normal limits. By December 1961 direct laryngoscopy revealed a considerable thickening of the epiglottis and a distal view of the vocal cords was almost impossible to obtain. During 1962, there was a considerable thickening of the tissues of the tongue and a general tightening of the mucous membranes of the pharynx and lips.

In December 1962, at the age of 14 he was 122 lb. and slightly obese for his height of 5 ft 2 in. By this time he had developed quite marked changes of the mouth and pharynx (Figs. 2a and b). An absence of the upper lateral incisors can also be seen. The nasal mucosa and ears were quite normal.

With direct laryngoscopy the true and false vocal cords appeared to form one solid block of tissue with a slightly irregular margin and without an intervening entricle. Under light anaesthesia this cordal mass was seen to be sluggishly mobile. An upper oesophagoscopy and a proctoscopy at the same time showed only normal mucosa.



FIG. 2. Gross specimen of the pharynx and post-pharyngeal wall.



Fig. 3. Tomogram of larynx showing loss of laryngeal ventricle with thickening of true and false vocal cords.

### Radiological Examination

Tomograms of the larynx showed that there was thickening of the ary epiglottic folds and boundaries of the pyriform fossae. It confirmed the laryngoscopic findings by showing the complete loss of a laryngeal ventricle due to thickening of both true and false vocal cords (Fig. 3). No abnormality was demonstrated in the sub-glottic region. An X-ray of the skull showed bilateral paracellar calcification and tomography confirmed the presence of two semilunar areas of calcification on either side of the pituitary fossa approximately 1.5 cm from the mid-line (Figs. 4 a and b). Air encephalograms carried out by Dr G. A. Steele showed that the calcified foci were seen to lie in the medial wall of the temporal horn anteriorly presumably in the hippocampus. The medial placed linear streaks appeared to lie in the cortex over the medial surface of the temporal lobe anteroinferiorly. The chest X-ray and the axial and paraxial skeletal X-rays were normal.

### Histology

The histological findings show the characteristic picture of lipoid proteinosis with an increase in hyaline material in the dermis causing narrowing of the rete peg of the epidermis, and the vessels are prominent due to



FIG. 11. Gross dissection of buccal cavity oropharynx and post-laryngeal wall.





FIG. 3. Tomograms of larynx showing loss of laryngeal ventricle with the healing of true and false vocal cords.

#### *Radiological Examination*

Tomograms of the larynx showed that there was thickening of the ary-epiglottic folds and boundaries of the pyriform fossae. It confirmed the laryngoscopic findings by showing the complete loss of a laryngeal ventricle due to thickening of both true and false vocal cords (Fig. 3). No abnormality was demonstrated in the sub-glottic region. An X-ray of the skull showed bilateral parasellar calcification and tomography confirmed the presence of two semilunar areas of calcification on either side of the pituitary fossa approximately 2.5 cm from the mid-line (Figs. 4 a and b). Air encephalograms carried out by Dr. G. A. Steele showed that the calcified foci were seen to lie in the medial wall of the temporal horn anteriorly, presumably in the hippocampus. The medially placed linear streaks appeared to lie in the cortex over the medial surface of the temporal lobe anteroinferiorly. The chest X-ray and the axial and paraxial skeletal X-rays were normal.

#### *Histology*

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FIG. 4 *a* and *b* Lateral view and APT micrograph showing bilaterally placed nuclei. There are two lipid droplets in the side.

a cuff of hyaline material around them (Fig. 5). Similar histological pictures have been reported by Ungar & Katzenellenbogen and by Laymon & Hill in 1957. McCusker & Caplan in 1962 have thought that the hyaline deposit in lipid proteinosis consisted of a glyco-protein with associated



FIG. 1. Biopsy from eyelid. (Haem. & Eosin.)

free or loosely bound lipid, and they suggested that the disorder should be more accurately labelled lipoglycoproteolysis.

#### *Biochemical and Blood Studies*

In December 1962, liver function tests including serum bilirubin, thymol turbidity, S.G.O.T., S.G.P.T., plasma proteins and their electrophoretic pattern were all normal. However, at that time the serum alkaline phosphatase was elevated at 35 units per 100 ml, though the serum calcium and serum inorganic phosphorus were normal. The glucose tolerance test and sensitive glucose tolerance test with Cortisone for latent diabetes were both negative, and the protein bound iodine and radio-iodine uptake showed no thyroid deficiency. Estimation of serum lipids, including serum free cholesterol, total fatty acids and neutral fat were within normal limits. The urinary calcium, inorganic phosphorus and the faecal fat were normal, though there was an occasional positive or weakly positive faecal occult blood. The C.S.F. and an electroencephalogram in December 1962 were normal, but in March 1963 an electroencephalogram reported that the delta activity was slightly more prominent and asymmetrical on the right than the left. Repeated estimations of the above tests of liver function showed no change from normality with the exception that the serum alkaline phosphatase level which remained at between 33 units and 38 units and in August 1963, increased to 52 units at the time when there was increased mobility of the tongue and improvement in the laryngeal picture.

Examination of the serum lipids of the father, mother and sister were

all normal but though the serum alkaline phosphatase of the parents was normal the sister's was repeatedly about 35 units/100 ml. The sister's liver function tests, serum calcium and phosphorus and X rays of the axial and paraxial skeleton were normal. Further examination of the brother now aged 18 years, recently in August 1966 showed no change in the clinical picture but for a slight loosening of the buccal and pharyngeal mucosa. Clinical examination of his sister aged 13 years, was normal. Biochemical tests of serum lipids, serum calcium and phosphorus were again normal in both, as were their liver function tests except for a raised serum alkaline phosphatase of 22 units in the brother and 20 units in the sister both showing liver isoenzyme activity.

### DISCUSSION

Some 20 cases of lipoid proteinosis have been described to date with endocranial calcification. Ramos e Silva in 1943 thought this occurred in the Dural Folds and since then it has been described in the temporal lobes, in the hippocampus and above the pituitary fossa (Caplan, 1962; Heyl, 1963; Dickey, 1964). By carrying out air encephalograms and tomograms it has been possible to localise more precisely the position of the calcification. In this case two areas of calcification can be clearly seen on either side of the mid line and it is possible that hitherto these have been interpreted as one.

Many attempts have been made to explain endocranial calcification and particularly of the basal ganglia in association with parathyroid deficiency. In the latter the clinical manifestations are the direct consequence of hypocalcaemia and hyperphosphataemia. The solubility product of calcium and phosphate ions tends to be elevated and osteoclastic activity is reduced so there may be some increased calcification of bone, and certain soft tissues, particularly the basal ganglia may show metastatic calcification. Milne in 1951 found a high concentration of phosphatase in the basal ganglia. In this case, repeated estimations of serum calcium and phosphorus were normal and the serum alkaline phosphatase was high. Could this have been sufficient to be related to the endocranial calcification in both hippocampal regions?

Extensive investigations of the consistently raised serum alkaline phosphatase of the boy and also of his sister failed to show any other evidence of liver or bony disorder. However since the alkaline phosphatase showed liver isoenzyme activity its raised level would seem to be indicative of an early involvement of the liver insufficient to show any abnormality in other liver function tests. Alternatively it has recently been shown by Warnock (1966) that there may be some functional similarity between endothelial phosphatase and that in the liver and the increased level may be related to the liberation of endothelial phosphatase in association with

the synthesis of lipoglycoprotein over a wide area of skin, mucous membrane and glandular tissue. It was noted in his case that there was an increase in serum alkaline phosphatase at the time when there was increased mobility of the tongue and larynx. It could be that the sister also has latent lipoid proteinosis, the already raised level of serum alkaline phosphatase in the sister who was without clinical changes, being explained by there being an equilibrium between the anabolic and catabolic processes in the formation of lipoglycoprotein. Cases have been reported in which lipoid proteinosis developed in a hitherto normal adult. In Sulzberger's case (1942) the changes appeared after a severe sore throat. The condition is also known to be familial and in those reported by Jensen (1932) and by Scott & Flindley (1959) it is seen that the clinical appearances occurred later in some members of the family than in others. Thus, it may be that if the sister is a case of latent lipoid proteinosis, even a severe upper respiratory infection may upset the balance of equilibrium and that she may yet develop clinical manifestations of lipoid proteinosis.

#### ACKNOWLEDGMENTS

My thanks are due to Professor V. F. Lambert and Mr. Verille Young for their help and ideas in preparing this paper and to Mr. W. L. Rowe of Beckett Hospital, Barnsley who originally referred this case to us. Also to Mr. Varley for the Biochemical investigation as Mr. S. Baker for the histological report. Dr. G. A. Steel for the Radiography and to Dr. Ollerenshaw Department of Medical Illustration, for the photographs.

#### ZUSAMMENFASSUNG

Die Eigenschaften von Lipoid-Proteinose die von besonderem Interesse für den Laryngologen sind, wurden dargestellt. Es wird angenommen, dass die erhöhte alkalische Serum-Phosphatase des beschriebenen Falles wohl die Folge der erhöhten Lipoglycoprotein-Synthese ist und dass nach längerer Zeit als weitere Folge endocraniale Kalkifikation auftreten kann. Die letztere ist hier zum erstenmal deutlich nachgewiesen worden. Es wird ebenso angenommen, dass innerhalb einer Familie der Lipoidproteinose nur bei einem Mitglied auftritt, eine erhöhte alkalische Serum-Phosphatase bei einem sonst klinisch offensichtlich gesunden Mitglied vielleicht als ein Anzeichen einer latenten Lipoidproteinose erstanden werden kann.

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## HISTOLOGICAL INVESTIGATIONS OF OTOSCLEROTIC FOCI

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A light microscope study of 237 temporal bones revealed 37 cases of definite histological otosclerosis. The incidence localization activity and number of otosclerotic foci are reported. The present material differs from previous similar studies of temporal bones in showing the incidence to be highest in the age range 65-80 years and the activity in the otosclerotic foci bear no relation to age. Furthermore the number of otosclerotic foci was largest in elderly persons.

Histological examination of temporal bones from patients with clinically manifest otosclerosis nearly always shows the otosclerotic foci to be localized around the oval window and to be accompanied by ankylosis of the stapes. According to several investigations, however histological otosclerosis in unselected materials is about 10 times as common as clinical otosclerosis (Engström, 1939; Guild, 1944; Nylen, 1949). In such investigations the frequency of stapedial ankylosis is lower as the majority of otosclerotic foci have not caused ankylosis of the stapes, even though they are localized to the anterior edge of the foramen ovale (Guild, 1944).

Otosclerosis is primarily a bone disease of the labyrinthine capsule, and the ankylosis of the stapes is an occasional complication which results in hearing impairment. We do not know why the lesion does not always encroach upon the annular ligament thus leading to stapedial ankylosis. Why the lesion only now and then affects the footplate of the stapes is an even greater mystery.

The operative treatment of otosclerosis has afforded a possibility of obtaining active otosclerotic bony tissue for histological examination unlike the previous studies of post mortem material. This has introduced new views on the pathogenesis of otosclerosis. It has been found, among other things, that active otosclerotic foci show signs of healing rather than of dissemination of the disease (Simson Hall 1963). Comparison of the clinical sign of progressing hearing impairment and the histological findings has shown that it is not the active, progressing disease which causes the hearing impairment, but the process of healing.

Increased interest in otosclerotic foci has, by histochemical and electron microscope studies in recent years (Cherance & Clerc, 1965 and Cherance, 1962) divulged further data concerning the histopathology of the disease.

Locally in histological foci abnormal quantities of mucopolysaccharides and increased amounts of alkaline phosphatase as well as sulph hydryl groups have been found. By electron microscopy Chevaunce demonstrated accumulation of acid mucopolysaccharides and simultaneous disintegration of the collagen fibrils. On the basis of these changes of the labyrinthine capsule and studies of the connective tissue in skin biopsies some authors (Arslan & Ricci 1963, Stadil 1961, Bentzen 1967) have suggested that otosclerosis should be interpreted as a local manifestation of a generalized connective-tissue disease. These new diagnostic methods have opened up new roads with interesting possibilities for elucidating the pathogenesis of otosclerosis.

In spite of the advanced technique within electron microscopy as well as histochemistry which have now been applied to the study of otosclerosis, classical light microscopy is still of interest, all the more so as such studies on major materials of temporal bones have in fact been rather sparse so far (cf. Nylen and Guild). We therefore felt that it might be of interest to report the findings in our material of temporal bones. In this study we laid stress on assessing the site, incidence, and activity of the otosclerotic foci.

### MATERIAL

The material comprises 237 temporal bones from 155 patients ranging in age from 1 month to 91 years. A certain selection of the temporal bones took place but not in respect to the occurrence of otosclerosis.

Table 1 lists the findings in those temporal bones in which we found otosclerosis.

### HISTOLOGICAL TECHNIQUE

The temporal bones were fixed in 10% neutral formalin, decalcified in a buffer solution of formic acid and sodium formate (Kristensen 1949) and embedded in celloidin. The prepared blocks were cut, on a special microtome, into sections of approx. 18  $\mu$ . All the preparations were cut in the horizontal plane, from the superior semicircular canal to the level of the cochlear aqueduct. Every 10th section was stained with haematoxylin-eosin. The remaining sections were stored. All stained sections were then studied systematically for otosclerosis.

### RESULTS

When speaking of otosclerosis it is important to distinguish between a clinical and a histological diagnosis, as also emphasized by Nylen (1949). Histological otosclerosis is often silent, as the disease does not cause hearing impairment until it has led to ankylosis of the stapes. None the less, there



may be otosclerotic changes, spread diffusely in the bony labyrinth, isolated at the round window or more centrally around the internal auditory canal. Such pathological changes cannot be revealed with certainty except by histology. However recent advances within radiology (in particular the introduction of tomography using a polytome) have afforded a possibility of demonstrating otosclerotics extending into the retrofenestral area (Mundnich, 1961; Jensen *et al.*, 1966; Valvassori 1966).

### *Incidence of Histological Otosclerosis*

Among the 82 patients for whom we have both temporal bones, we found bilateral otosclerosis in 8 (9.7%) and unilateral otosclerosis in 5 (6%). Among 73 patients for whom we have only one temporal bone otosclerosis was present in 8 (8%).

Thus, among the 237 temporal bones we found otosclerosis in 27 (11.4%)—from 19 patients. Of these patients 14 were males (13.6%) and 5 females (8.3%).

The present material hardly permits any definite conclusion concerning the incidence of otosclerosis in men and women. As is well-known, clinical otosclerosis is about twice as common in women as in men. Engström and Nylen found histological otosclerosis to be about equally common in both sexes. We are unable to confirm their finding. On the contrary our material showed a male preponderance (Jørgensen & Kristensen, 1967).

Unlike Guild (1944) we did not find otosclerosis in children. Our youngest case was a woman aged 28.

### *Localization of otosclerotic foci*

The localization of the otosclerotic changes is shown in Table 1. In 26 (96%) of the 27 cases the process was localized around the oval window in most cases anterior to the oval window extending a varying distance to the posterior aspect above or below the window.

In 5 cases (19%) the otosclerotic process around the oval window was accompanied by fixation of the stapes resulting in ankylosis, while in 16 (59%) of the 26 cases there were attendant otosclerotic changes of the stapes, but without ankylosis.

We have not found any cases with otosclerotic changes exclusively of the stapes or in the other ossicles.

In 11 cases (41%) the otosclerotic foci at the oval window were accompanied by a focus at the round window. However these foci were confluent in only 3 cases (17%).

From these figures it may be seen that the regions around the oval and the round window are involved in the majority of cases. This is in keeping with previous experience.

We found the cochlear capsule to be involved in 7 cases (26%) and in 2

TABLE 1 *Histological findings in 27 otosclerotic temporal bones*

Case no.	No of temporal bones	Age	Sex	Side	Oval window	Stapes	Fixation	Round window	Cochlear capul	Meatus acusticus int rna	Area outside the labyrinthine bone capsule	Activity of the loose ot focus	No of otosclerotic foci
1	2	28	F	r	+	+						++	2
				l	+	+						++	1
2	2	37	M	r									
				l	+	+		+				++	1
3	2	40	M	r	+							++	1
				l									
4	1	47	M	l							+	+	1
5	1	50	M	l	+	+		+				+++	1
6	2	55	M	r									
				l	+	+						+	1
7	1	58	F	l	+							++	1
8	2	61	M	r	+							+	1
				l									
9	2	63	M	r	+	+			+			++	1
				l	+	+						++	1
10	2	64	M	r	+							++	1
				l	+							++	1
11	1	65	M	l	+							+	1
12	2	60	M	r	+							+	1
				l	+						+	+	1
13	2	70	F	r	+	+		+				+++	2
				l	+	+		+				+++	3
14	1	70	F	r	+	+		+	+	+		+++	1
15	2	71	M	r	+	+	+	+	+			+++	2
				l	+	+	+	+	+			+++	1
16	2	75	M	r	+	+	+	+	+			+++	1
				l	+	+	+	+	+			+++	1
17	1	79	F	r	+	+	+	+	+	+		+++	2
18	2	87	M	r	+	+	+					++	1
				l									
19	2	91	M	r	+		+	+				+++	2
				l	+							++	1

cases (7%) the foci were at the floor of the internal acoustic meatus. Accordingly other parts of the bony labyrinthine capsule are involved in a large number of cases.

In 2 instances we found otosclerotic foci outside the capsule of the bony labyrinth. One was an isolated otosclerotic focus in the lateral semicircular

canal of a 47 year-old man whose condition had been diagnosed as Menière's disease. The other patient was a 60-year-old man with a history of radical mastoidectomy in whom the vestibule was found to be overgrown with connective tissue which, in a large marginal zone, had ossified into tissue of the otosclerotic type. These changes had continued into the cochlea where the scala tympani, vestibule and cochlear duct were replaced by vascular bony tissue of a mosaic pattern in the lower two-thirds of the cochlea.

As a rule the localization of the bilateral foci was symmetrical in both temporal bones.

Unilateral otosclerosis was found in 5 out of 13 patients for whom we have both temporal bones. This gives a somewhat higher percental distribution than shown by previous studies (Nylén and Gullö) as usually the incidence of unilateral otosclerosis is stated to be 15-30%.

Pathological bony changes, the so-called "blue mantles" were found by us not only in otosclerotic temporal bones, but also in temporal bones without otosclerotic foci. In that case we considered the finding negative.

#### *Activity of the otosclerotic foci*

As is well-known, otosclerosis may be present clinically as well as histologically in various stages of activity. We have grouped the histological activity as +, ++ and +++ according to whether the foci showed low, medium, or high activity. When several stages were represented in the same temporal bone the preparation was classified according to the highest activity present.

We found almost the same number of cases showing foci with high activity (10 cases) and medium activity (11 cases). Only 6 cases were classified in the group of low activity. The activity in bilateral foci was nearly always the same.

Table 1 shows, moreover, that active otosclerotic foci were found in the temporal bones of elderly patients, at variance with the current opinion (Jørgensen & Kristensen, 1967).

#### *Number of otosclerotic foci*

In 21 temporal bones (78%) we found only one focus. This incidence of single foci is somewhat higher than that reported by others. In the remaining 6 temporal bones we found 2 foci in five and 3 foci in one. We did not encounter more than 3 foci in any temporal bone.

It has previously been believed (Nylén, 1949) that advancing age, and possibly continued growth of a focus, will tend to the fusion of several foci, so that the number of foci decreased after the age of 50. This is not confirmed by our material. On the contrary the number of foci appears to be largest in the elderly. 5 of the 6 temporal bones with more than one focus being derived from patients 6 or 70 years of age.

## DISCUSSION

In a study of temporal bones for otosclerosis we made several findings of interest. In the first place we found the highest incidence in the age range 60-80 years (17.7%) (Jørgensen & Kristensen 1967) while Guild (1944) found the highest incidence in the age group 30-50. Secondly we found that the activity in the otosclerotic foci did not decrease with advancing age. For instance, we found a highly active focus in a man aged 91. Thirdly we found the number of foci within each temporal bone to be largest in elderly patients.

It seems probable, then, that active otosclerosis is just as common in elderly as in younger persons and that ankylosis of the stapes is possible, at least theoretically, at any time of life.

It would be very interesting to investigate a material sufficiently large to permit statistical conclusions as to whether the number and activity of otosclerotic foci increases or decreases with advancing age. The latter view appears to prevail.

It is known that otosclerosis may give rise to vertigo, tinnitus, and perceptible hearing loss—even in the absence of stapedial ankylosis. Even conditions interpreted as Menière's disease have turned out to be otosclerosis (Paparella & Chasin 1966).

We feel therefore that our findings must stimulate to increasing the efforts at further investigation in cases presenting diagnostic difficulties, especially in elderly patients.

Today we have no clinical method for ascertaining the degree of activity in otosclerotic foci in the area of the foot plate. For instance, a positive Schwartze phenomenon merely indicates that a focus is active in the promontorial area, but not necessarily around the foramen ovale.

Without doubt a number of cases can be disclosed by tomography using the polytome, but a more detailed investigation can be done only by exploratory tympanotomy. This is a procedure which, even in the elderly, causes little discomfort and which will no doubt be used with increasing frequency in the future.

## ZUSAMMENFASSUNG

Lichtmikroskopische Untersuchungen von 237 Schläfenbeinen ergaben 27 Fälle mit sicher histologischer Otoasklerose. Die Inzidenz, Lokalisation, Aktivität und Anzahl von otosklerotischen Foki wurden beschrieben. Unser Material unterscheidet sich von früheren ähnlichen Schläfenbeinuntersuchungen, indem wir die grösste Inzidenz in der Altersgruppe von 60 bis 80 Jahren gefunden haben. Die Aktivität in der otosklerotischen Foki steht in keinem Verhältnis zum Alter. Ferner finden wir die grösste Anzahl der otosklerotischen Foki bei älteren Menschen.

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## DISCRIMINATION IN ELECTRIC TASTE

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Taste discrimination is measured by using electric taste stimuli. The results obtained from six subjects at three intensity levels support the contention that the size of differential threshold grows as a power function of stimulus intensity the exponent being 0.4. For the Weber ratio an average value of 0.14 was obtained. This value lies close to the 0.13 for salt as reported in the literature. When calculated and interpolated from the results 17 successive jnds were obtained up to the stimulus intensity of 120  $\mu$ A. Beldler's function was approximately linear from the 4th jnd onward.

Discrimination in any perceptual modality is one of the factors on which the amount of information input depends. Experiments on discrimination in gustation have been under study for about one hundred years since in 1860 Keppler published his first observations on differential thresholds (also called just noticeable difference, jnd  $\Delta I$ ) in taste. He studied the validity of Weber's law in gustatory perception and came to the conclusion that his results did not support the law.

Since his time a number of papers have been published investigating the same basic question. Various opinions have been expressed as to the validity of Weber's law. Lemberger (1908) found deviation from the law in the upper and lower ranges. Fodor & Happlach (1922) agreed that the law is valid in the middle range. Saidullah (1927) obtained results which support the law in the case of salt, one of the four basic taste qualities. Kopera's results (1931) support the law but his Weber ratios are different for different stimulus solutions even of the same quality. Bujas (1937) obtained constant Weber ratios for salt, sweet and sour whereas Schutz & Pilgrim (1937) stated that the law was valid for bitter and found only slight deviations for the other taste qualities.

Studying jnds for salt Beldler (1961) obtained a linear correlation between the ratio  $(C/R)$  and  $(C)$  ( $C$  being the concentration of the solution and  $R$  being the cumulative number of jnds).

One of the latest studies on taste discrimination is that of Fischer *et al* (1965). They report that the jnds from Lemberger's data are linear in a log-log plot between the 7th and the 38th jnd, the axes being concentration of solution and size of jnd. This exponential function was already theoretic

eally proposed by Pütter in 1918. In their own experiments they find a constant for the Weber ratio for sucrose and sodium saccharinate.

Furthermore Fischer *et al.* (1963) found the number of successive judgments as big as 40. In calculating the information capacity of the gustatory system v. Skramlik (1963) states that every taste quality possesses 20 successive judgments.

The sizes of the relative differential thresholds ( $\Delta I/I$ ) Weber ratios, in the various taste qualities are given by Pfaffmann (1959) on the basis of the studies up to that time. They are also reproduced by Hensel (1966). According to him the mean values for the different taste qualities are 0.20 for sweet, 0.15 for salt, 0.25 for bitter and 0.21 for sour. Fischer *et al.* (1963) report the value of 0.41 for sucrose. Great interindividual variations occur as shown for instance by the experiments of Schutz & Pilgrim (1957).

All these studies on taste discrimination have been conducted by using chemical stimuli for the four taste qualities. In the past years, however, electric stimulation of the tongue has become of great importance because it is especially applicable in clinical testing of taste acuity. Electrogustometers have been constructed in various otological centers to deliver suitable electric pulses. Electric stimulation of taste has been known since the time of Sulzer (1754). Both a.c. and d.c. stimulation have been proved to be effective, and in fact v. Békésy (1964) obtained all four taste qualities by appropriate a.c. stimulation of various intensities and frequencies. A simple clinical electrogustometer on the other hand employs mostly d.c. stimuli and no special attention is paid to the quality of taste sensation evoked. With normal d.c. stimuli usually a sour-salty sensation is reported, but additionally there may be also bitter components.

Studying discrimination in taste, Bujas (1937) used also electric stimulation. On the basis of his results he came to the conclusion that the Weber ratio for electric taste is not constant, but grows with increasing stimulus intensity.

## METHODS

The purpose of the present study was to measure differential thresholds of the electric taste using a conventional clinical electrogustometer.

The electrogustometer used was developed at the Helsinki University Otolaryngological Hospital for routine clinical taste testing. The circuit diagram of this device has been published elsewhere (Jauchlainen *et al.* 1967). With this electrogustometer d.c. stimuli ranging from 30 to 90  $\mu A$  were delivered from the electrodes to the tip of the tongue of the subject.

The task of the subject was to assess whether a test stimulus of about 1 sec duration given 2 sec after a standard stimulus of the same duration was stronger or weaker than the standard. Test stimuli on both sides of

the standard were delivered in random order with three presentations of each stimulus until a value was reached where two of the three were reported different stronger or weaker respectively. Three stimulus ranges were used 30 50 and 90  $\mu$ A.

Six of the hospital staff served as volunteers, each in six sessions, one session lasting 10 to 15 minutes.

## RESULTS

With the above mentioned technique a descending and an ascending differential threshold was obtained for every stimulus intensity. The arithmetic means of the differential thresholds ( $\Delta I$ ) and their standard deviations (s.d.) are given in Table 1. Table 2 shows the Weber ratios ( $\Delta I/I$ ) calculated from the thresholds.

TABLE 1 *Differential thresholds ( $\Delta I$ ) for electric taste stimulation in microamperes*

Desc. = Descending threshold; Asc. = Ascending threshold.

Subject	Intensity level														
	30 $\mu$ A					50 $\mu$ A					90 $\mu$ A				
	Desc.	s.d.	Asc.	s.d.	Mean	Desc.	s.d.	Asc.	s.d.	Mean	Desc.	s.d.	Asc.	s.d.	Mean
h.	6.7	0.2	5.0	0.0	5.9	9.2	0.5	5.8	0.2	7.5	10.0	0.4	6.7	0.2	8.1
L.	5.8	0.2	5.8	0.2	5.8	9.1	0.4	5.9	0.0	7.1	15.9	0.5	5.0	0.0	10.5
L.	5.8	0.2	5.8	0.2	5.8	10.8	0.4	5.8	0.2	8.3	10.0	0.5	7.5	0.3	8.8
i	5.0	0.0	5.0	0.0	5.0	5.0	0.0	5.8	0.2	5.4	9.1	0.4	5.8	0.2	7.3
u	5.8	0.2	6.7	0.4	6.3	7.5	0.4	5.8	0.2	6.7	10.0	0.6	5.0	0.0	7.5
L.	5.8	0.2	6.0	0.0	5.4	6.7	0.2	5.0	0.0	5.9	6.7	0.2	5.8	0.2	8.1
Mean	5.8		5.6		5.7	8.1		5.5		6.8	12.8		6.0		8.1
s.d.	0.58		0.76		0.50	2.28		0.46		1.34	3.32		1.08		1.60

TABLE 2 *The relative differential thresholds Weber ratio ( $\Delta I/I$ ) for electric taste stimulation*

Subject	Intensity level								
	30 $\mu$ A			50 $\mu$ A			90 $\mu$ A		
	Desc.	Asc.	Mean	Desc.	Asc.	Mean	Desc.	Asc.	Mean
Ah.	0.23	0.17	0.20	0.18	0.12	0.15	0.11	0.07	0.09
AL	0.19	0.19	0.19	0.18	0.10	0.14	0.17	0.06	0.12
Ja.	0.19	0.19	0.19	0.22	0.12	0.17	0.11	0.03	0.10
Ju.	0.17	0.17	0.17	0.10	0.12	0.11	0.10	0.06	0.08
Nu.	0.19	0.22	0.21	0.15	0.12	0.13	0.11	0.06	0.08
PL	0.19	0.17	0.18	0.13	0.10	0.12	0.07	0.06	0.07
Mean	0.19	0.19	0.19	0.16	0.11	0.14	0.12	0.07	0.09
s.d.	0.018	0.022	0.016	0.046	0.012	0.024	0.036	0.010	0.020



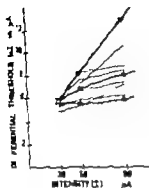


FIG. 1

FIG. 1 The means of differential thresholds for the electric taste plotted in linear coordinates against function of stimulus intensity. The circles (○) give the mean differential thresholds, the downward pointing triangles (▽) the descending differential thresholds, and the upward pointing triangles (Δ) the ascending ones. The thick lines give the mean differential thresholds for each subject.

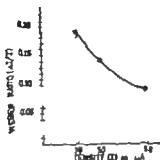


FIG. 2

FIG. 2 The Weber ratios plotted as function of stimulus intensity in linear coordinate system. The dots give the means for each subject and the open circles the means of all the subjects.

When the results are plotted in a linear coordinate system, curves are obtained, which show that the Weber ratio is not constant, but a declining function with increasing stimulus intensity. Figures 1 and 2 provide the graphs in linear coordinate systems. Figure 3 gives the plot of differential thresholds as a function of stimulus intensity in a log-log-coordinate system whereby a straight line results. When the slope of this function is calculated the value of 0.4 is obtained.

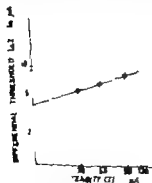


FIG. 3

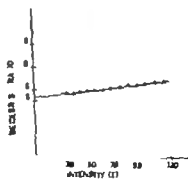


FIG. 4

FIG. 3 The means of differential thresholds plotted in log-log-coordinate system as function of stimulus intensity. The dots give the means for each subject.

FIG. 4 The Weber ratio plotted as function of stimulus intensity plotted on log-log coordinates.

In order to get the Beldler's ratio the cumulative number of differential thresholds is calculated and interpolated from the results presented in Fig. 3. When the calculation is started from 10  $\mu\text{A}$ , a value lying not far from the average threshold value (Krarup 1958) 17 successive thresholds are obtained up to the intensity of 120  $\mu\text{A}$ . The Beldler's ratios ( $C/R$ ) are plotted in respect to the intensity level ( $I$ ) in a coordinate system in Fig. 4. A linear relation is obtained from the 3rd or 4th jnd upward.

### DISCUSSION

The Weber ratio obtained by electric taste stimulation approximates the value 0.14. This result agrees rather well with the 0.15 given in the literature for chemical stimulation by salt. After all, electric stimulation of taste receptors evokes a sensation not far from salty.

When the differential thresholds are plotted in a log-log-coordinate system, a straight line results. That corresponds with the idea that in electric taste stimulation the size of the just noticeable difference grows as a power function of the stimulus intensity.

The cumulative number of jnds, as calculated from our results, is 17. This is in a rather good agreement with the value of 20 given by S. Skramlik (1963). The upper limit of 120  $\mu\text{A}$  has been taken in the present calculation because the intensity function of electric taste was obtained as a power function up to the intensity of 120  $\mu\text{A}$  (Jauhainen *et al.*, 1967). The change of the slope of this intensity function at that value possibly reflects the maximum of taste sensation, as discussed in the previous study.

The results also show the differences of descending and ascending threshold values. From this study it can clearly be seen that the difference to a decrease of stimulus intensity is more difficult to detect than to an increase.

In the previous study the authors obtained for the slope of the power function of electric taste the value of 1.2. This number and the exponent of the power function for jnds together characterize the information capacity of the gustatory system with electric stimulation.

### ZUSAMMENFASSUNG

Das Unterscheidungsvermögen des Geschmackssinnes wird für elektrische Reizung der Zunge gemessen. Die an sechs Versuchspersonen bei drei Intensitätsstufen gewonnenen Ergebnisse stimmen mit der Vorstellung überein, dass der eben merkliche Reizzuwachs ( $\Delta I$ ) als Potenzfunktion der Reizstärke zunimmt (Exponent 0.4). Die Unterschiedsschwellen ( $\Delta I/I$ ) weisen einen Mittelwert von 0.14 auf, der nahe dem in der Literatur beschriebenen Wert für Salz (0.15) liegt. Aus den Ergebnissen werden bis zu einer Reizstärke von 120  $\mu\text{A}$  17 aufeinanderfolgende Unterschiedsschwellen berechnet. Die Beldler-Funktion ist von der 4. Unterschiedsschwelle an näherungsweise linear.

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## RETURN EYE MOVEMENTS, SACCADIC MOVEMENTS, AND THE QUICK PHASE OF NYSTAGMUS

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Electric stimulation of ampullary nerves in the alert cat and monkey induces active diphasic eye movements. These consist of an initial deviation followed by a movement which returns the eyes toward or past their initial position in the orbit. The second movement has been designated a return eye movement and is a central oculomotor reflex. This reflex appears to provide ocular compensation for head movements induced by strong impulses of angular acceleration. Modulating influences on this reflex include vision, head and eye movements, the initial position of the eyes in the orbit and the head on the neck, and the level of alertness. There is a reciprocal relationship between the amplitude of initial deviations and active return movements which varies linearly with changes in eye position. Characteristics of return movements link them closely to saccadic movements and the quick phase of nystagmus, and differentiate them from other compensatory eye movements which have been previously described.

### INTRODUCTION

We have previously shown that eye movements which follow ampullary nerve stimulation in the alert cat or monkey are bidirectional (Cohen *et al* 1967). The eyes initially deviate in a movement analogous to a tonic deviation or single slow phase of nystagmus. This is followed by an active movement in the opposite direction which returns the eyes toward or past their initial position in the orbit. This second movement, termed a "return eye movement," is a central oculomotor reflex. It appears to coordinate compensatory head and eye movements during strong impulses of angular acceleration.

This reflex is presumed to act in the following way. When an impulse of angular acceleration or an ampullary nerve stimulus is weak, then an eye movement alone may provide satisfactory compensation. When a stimulus is strong, however, then compensatory movements of both the

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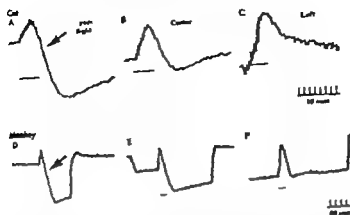


FIG. 1. Effects of eye position, initial deviation, and return eye movement in cat (A-C) and monkey (D-F). Animals were in light with head restrained. The EOG was recorded heteropolarly with DC-coupling. The left lateral semicircular canal nerve was electrically stimulated for the period shown by the horizontal bar under each trace. An upward deflection of the trace (1st and subsequent figures indicates) a eye movement to the right. Return movement in A and D are marked by arrows. The time base for A-C is 10 msec per time marker shown under C, and for D-F is 50 msec per time marker shown under F. The initial deviation in C is about 15° and in F is about 20°.

head and eyes are induced. First the eyes move. Then as the head begins to move, the eyes flick rapidly in the opposite direction to counter the head movement. The rapid counter-deviation of the eyes is the return eye movement. Without it summation of a head and eye movement in the same direction would probably result in overcompensation of the gaze angle. Return movements are similar to the "anticompensatory eye movements" of Jones (1964). Thus the reflex is probably also present in humans.

In this report the analysis of return eye movements has been extended. Data is presented to show how the reflex is modulated and to demonstrate basic similarities which exist between return eye movements, saccadic movements, and the quick phase of nystagmus. From these data some properties of the neural organizations which initiate rapid eye movements have been inferred.

#### METHODS

Alert unanesthetized cats and monkeys (*Macaca mulatta*) were used. Eye and head movements were induced by stimulating semicircular canal nerves with 50 msec trains of 0.5 msec square waves at an intra-train frequency of 500/sec. Complete details of electrode implantation and methods of stimulation have been given in previous publications (Cohen, Suzuki & Bender 1964, 1965; Suzuki, Cohen & Bender 1964a, b; Cohen, Tokumasa & Goto, 1968; Suzuki & Cohen, 1966). Although return eye movements are similar when any of the canal nerves are activated, for convenience only results of left lateral canal nerve stimulation will be

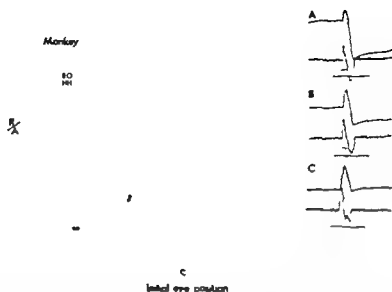


FIG. 2 Relationship between amplitude of initial deviation and return movements  $R$  and initial eye position. A-C show eye movements induced from right, center and left initial eye positions, respectively. The top trace of each pair is the DC-EOG. The bottom trace is the differentiated EOG. The room was illuminated for the period shown by the lower longer horizontal bar under each pair of traces. The pupillary nerve stimulus is signalled by the upper shorter horizontal bar (see Method for detail). The largest return movement (in A) is about 45°. In the graph on the left the ratio  $R/A$  is shown on the ordinate and eye position on the abscissa. The letters L and R represent about 20° of original eye deviation to left and right.

described. Such stimulation induces an initial eye and head deviation to the right and a return eye movement to the left in both cat and monkey (Cohen *et al.* 1967).

Eye movements were recorded by registering changes in the corneo-retinal potential (EOG) across both eyes either with RC-coupling with a 3 sec time constant or with DC-coupling. In each of the succeeding figures an eye movement to the right is shown by an upward deflection of the trace. The EOG was differentiated by an amplifier with a 0.002 sec time constant. In Fig. 9 the differentiated record was rectified and amplified, and the velocity of the return movements was displayed alone in the third channel. Eye movement recordings were taken with animals in the light (EO) or dark (EC) and with the head free (HF) or restrained (HH). The EEG was monitored in some cases using conventional technique.

In two experiments special conditions were used.

(1) In Fig. 2 initial deviations and return eye movements were analyzed after a monkey had moved its eyes to different positions of fixation. For this analysis it was necessary to reduce the spontaneous saccadic shifts without decreasing alertness and to direct gaze in desired directions. This was accomplished by placing the animal in a darkened room. A dim light was briefly exposed. When it attracted the monkey's attention it was extinguished and an oscilloscope trace was begun. Sample traces of eye movements are shown in Fig. 2A-C. The sweep triggered a light which

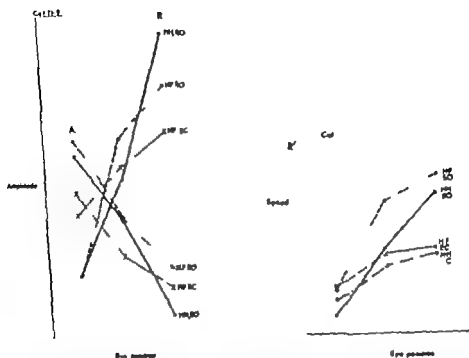


FIG. 2. Graphs showing the effect of eye position on amplitude of initial deviation  $A$  and return movement  $R$  (left) and on velocity of return movement  $R'$  (right). Data were taken from DC-EOG. Animals were in light (EO) or dark (EC) with their heads free (HF) or restrained (HH).  $L$  and  $R$  represent approximately  $30^\circ$  of initial deviation of the eyes to left and right in both graphs. Each point represents the mean of approximately 30 samples. The maximum difference between  $A$  and  $R$  under HH-EO conditions is about  $30^\circ$ .

Illuminated the room for the period indicated by the longer horizontal bar under each pair of traces. 100 msec after the onset of this light a 50 msec train of impulses was delivered to the left ampullary nerve (shorter horizontal bar). This proved to be effective in maintaining the monkey's attention. Both the initial deviation and return movement occurred in the light.

(2) In Fig. 3 return movements were induced during spontaneous nystagmus. This nystagmus followed a small vestibular nucleus lesion and was present only in the dark. This lesion did not disturb the pattern of canal nerve-induced eye movements.

### RESULTS

As previously demonstrated return eye movements were largest in both cat and monkey when vision was present. In addition return movements were larger and faster in the cat when the head was free to move. Other factors which affected return eye movements included

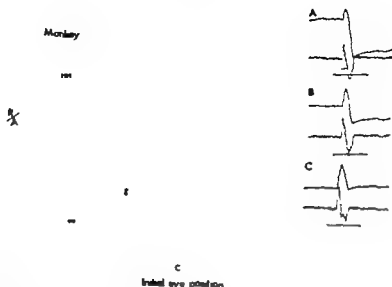


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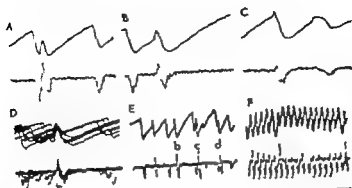


FIG. 5. Return eye movements during spontaneous nystagmus. Monkey in dark with head restrained. Upper trace is the AC-EOG. Lower trace is the differentiated EOG. Left lateral canal nerve stimulus is shown by the horizontal bar or dots underlying the lower trace of each pair (see Methods for details). In A-D stimulus artifacts are the time base (50 msec). Time base for E and F is 1 second, shown under F. Beats of nystagmus are approximately  $30^\circ$  amplitude. A-C, initial deviations and return movements induced at various times during the nystagmus cycle; D superimposed traces similar to A-C; E and F make the entire time base. E, ampullary nerve stimulated at a-d; F, ampullary nerve stimulated at 1-5 trains per second.

than grouping the absolute values of R or A. The ratio R/A tended to be linearly related to the position of the eyes in the orbit (Graph, Fig. 2).

The tendency toward a reciprocal relationship between initial deviations and return eye movements in different eye positions was present in both cat and monkey with the head free or restrained and with or without vision. This is demonstrated in Fig. 3. The graph on the left shows the effect of eye position on the amplitude of initial deviations (A) and return movements (R). On the right is graphed the effect of eye position on velocity of return movements (R). Consistent with previous findings (Cohen *et al.* 1967) the amplitude and velocity of return movements tended to be somewhat larger in the light than in the dark.

### Eye movement

Effects of eye movement on initial deviations and return movements were different depending on whether the ongoing eye movement was slow or rapid in character. If rapid, either the initial deviation or return eye movement blended into the ongoing rapid eye movement if they were in the same direction or tended to be suppressed if they were in opposite directions. This is shown in Fig. 4 B and C during saccadic movements and in Fig. 5 E during the quick phase of nystagmus (in response to the d<sup>+</sup> stimulus). In contrast when the ampullary nerve stimulus fell during a slow movement, as for example a slow phase of nystagmus (Fig. 5 A-C) then the reciprocal relationship between initial deviations and return eye movements dependent on initial eye position was similar to that found when the eyes were still. Soon after the end of a rapid movement, biphasic

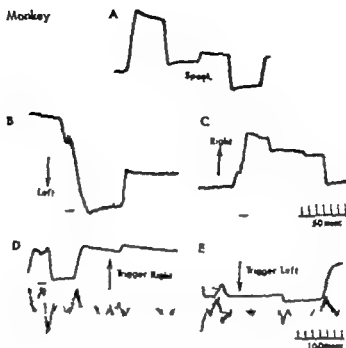


FIG. 4. Return movement induced during saccadic movements and fixation in light with head fixed. Ampullary nerve pulse train of 50 msec duration are shown by horizontal bars in B-E. A spontaneous saccade shifts B and C ampullary nerve stimulation during saccadic movement. Arrows (left and right) indicate direction of ongoing saccadic movement. D an eye movement to the right and E an eye movement to the left were used to trigger the stimulus. The lower traces in D and E are the differentiated EOG. The time base for A-C is 50 msec per time marker shown under C and for D and E is 100 msec per time marker shown under E. The vertical arrows represent approximately 15° of eye movement in B and C and 30° in D and E.

### Eye position

The initial position of the eyes in the orbit affected both the amplitude and velocity of initial deviations and return eye movements (Fig. 1). In both cat and monkey when the eyes were originally turned in the direction of the initial deviation i.e. to the right (A and D) then the initial deviation was small and the return eye movement was large. The converse was true when the eyes were originally away from the direction of the initial deviation i.e. to the left (Fig. 1 C and F). In this case the initial deviation was large and the return movement was small. The latency of return movements was shorter when the eyes were in the direction of the initial deviation (Fig. 1 A) than when they were away from it (Fig. 1 B or C). The minimum latency of return movements was about 30 msec when the animals were in the light (Fig. 1 A).

The relationship between eye position, initial deviations, and return movements was analyzed in the monkey. Because successive eye movements from the same initial position varied somewhat in size, the ratio of the amplitude of the return movement induced by a single pulse train over the initial deviation from the same stimulus ( $R/A$ ) was determined rather

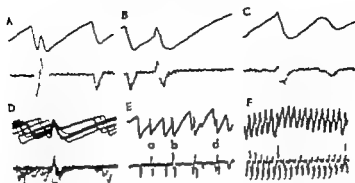


FIG. 3. Return eye movements during spontaneous nystagmus. Monkey 1, dark with head restrained. Upper trace is the RC-EOG. Lower traces are the differentiated EOG. Left lateral canal nerve stimulation is shown by the horizontal bar or dots underlying the lower trace of each pair (see Methods for detail). In A-D stimulus artifacts are the time base (50 msec). Time base for E and F is 1 second, shown under F. Beats of nystagmus are approximately 18° in amplitude. A-C, initial deviation and return movements induced at various times during the nystagmus cycle. D, superimposed traces similar to A-C; E and F show slower time base. E, ampullary nerve stimulated at a-d. F, ampullary nerve stimulated at 1-4 trains per second.

than grouping the absolute values of R or A. The ratio R/A tended to be linearly related to the position of the eyes in the orbit (Graph, Fig. 2).

The tendency toward a reciprocal relationship between initial deviations and return eye movements in different eye positions was present in both cat and monkey with the head free or restrained and with or without vision. This is demonstrated in Fig. 3. The graph on the left shows the effect of eye position on the amplitude of initial deviations (A) and return movements (R). On the right is graphed the effect of eye position on velocity of return movements (R). Consistent with previous findings (Cohen *et al.* 1967) the amplitude and velocity of return movements tended to be somewhat larger in the light than in the dark.

#### Eye movement

Effects of eye movement on initial deviations and return movements were different depending on whether the ongoing eye movement was slow or rapid in character. If rapid, either the initial deviation or return eye movement blended into the ongoing rapid eye movement if they were in the same direction or tended to be suppressed if they were in opposite directions. This is shown in Fig. 4 B and C during saccadic movements and in Fig. 5 E during the quick phase of nystagmus (in response to the "d" stimulus). In contrast when the ampullary nerve stimulus fell during a slow movement, as for example a slow phase of nystagmus (Fig. 5 A-C) then the reciprocal relationship between initial deviations and return eye movements dependent on initial eye position was similar to that found when the eyes were still. Soon after the end of a rapid movement, biphasic

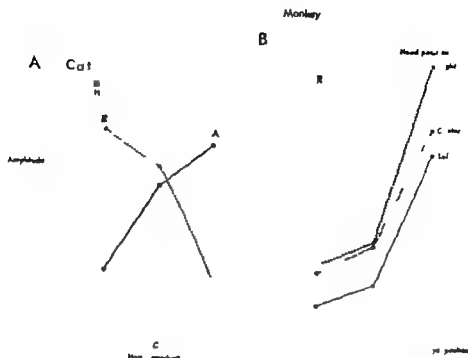


FIG. 6. Graphs showing the effect of head position on initial deviations and return eye movements. Each point represents the mean of 30 samples of DC-EOG's. Animals were in light with head centered or turned 35° to right or left. Movements in graph on left were taken with eyes in midposition. The maximum difference between A's or R's of 90° of head position change was about 6°. Effects of eye and head position on return movements from different eye positions are shown in graph on right. L and R present initial eye positions of 30° to left and right. There is approximately 30° of difference between the maximum and minimum return movements.

eye movements dependent on initial eye position were again evoked by ampullary nerve stimulation (Fig. 4D and E).

It is apparent in Fig. 4D that return movements resembled saccadic movements when evoked from a stationary eye position. On the other hand, return movements evoked during slow eye movements were identical in form and velocity to single quick phases of nystagmus (Fig. 5D and E). When return movements were induced more rapidly, artificial nystagmus could be produced when the frequency of the pulse train repetition rate was about 4 per second (Fig. 5F). The initial deviations in this case were small but were present at the apex of each beat. They are shown by the upward deflection of the velocity trace at the onset of each stimulus. Four beats per second is close to the frequency of steady state nystagmus induced by ampullary nerve stimulation in the cat (Cohen, Suzuki & Bender 1965). Cycling of artificial nystagmus may have been aided by suppression of succeeding quick phases after each return movement which lasted for several hundred milliseconds (Fig. 6D). Saccadic movements were also suppressed after return movements induced from a position of fixation. This is particularly apparent in Fig. 4D but is present after each return

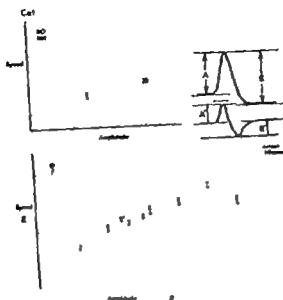


FIG. 7. Graph of relationship of amplitude and locality of initial deviations ( $A$  and  $A'$ ) and return eye movement ( $B$  and  $B'$ ) in cat. Each dot represents one eye movement. Techniques for measuring amplitude and locality are shown in insert on tracings of DC and differentiated EOG.

movement (Fig. 1 D-F 4 E, and Fig. 8 of Cohen Goto & Tokumasa 1967).

#### Head position

Effects of head position on initial deviations and return eye movements was similar to effects of eye position. That is, initial deviations tended to be smaller and return eye movements larger when the head was turned in the direction of the initial head or eye movement (to the right) than when it was turned away from this direction (to the left). This is shown in the graph of Fig. 6 A. In both monkey and cat the effect of head position on return movements was considerably less than eye position but could be demonstrated whether the eyes were initially centered, to the right, or to the left (Fig. 6 B).

#### Relationship to other rapid eye movements

A number of similarities linked return eye movements, saccadic movements, and quick phases of nystagmus.

- (1) Return movements resembled saccadic movements when generated from a position of fixation (Fig. 4 D) and quick phases of nystagmus when induced during pursuit movements or slow phases of nystagmus (Fig. 5).
- (2) There tended to be occlusive interaction between return movements and saccades or quick phases of nystagmus as well as suppression of other

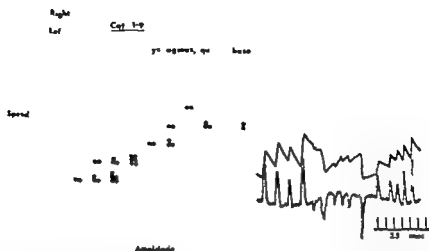


FIG. 8 Relationship between amplitude and velocity of quick phases of nystagmus in cat. Nystagmus induced by pendular rotation in light first right, then left, and again in right. The RC-EOG (top trace) and differentiated EOG (bottom trace) are shown in the insert. Time base is 250 msec per time mark. Largest beats of nystagmus were approximately 30° in amplitude. Each dot in the graph represents one eye movement, closed circles being quick phases to right and open circles quick phases to left.

rapid eye movements after return movements (Figs. 4 and 5). Return movements and slow movements did not interact similarly.

(3) There tended to be a linear relationship between amplitude and peak velocity of return movements (Fig. 7 lower graph). This also tends to be true for saccadic movements and quick phases of nystagmus in humans.

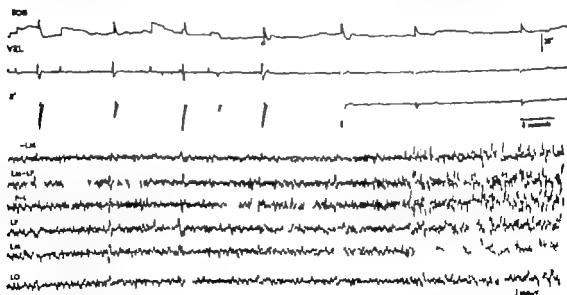


FIG. 9 Effects of alertness on initial deviation and turn eye movement in monkey. Top trace is the DC-EOG, second trace the differentiated EOG, and third trace the differentiated EOG which was amplified and rectified to display velocity of return movements in isolation. Below are six derivations of the EEG. Left lateral canaliculus stimuli given at point a-g.



FIG. 10. Effects of alertness, drowsiness, and sleep on initial deviations and return eye movements in monkey 2 perimposed tracings in light with head restrained. Horizontal line under C is 100 msec and vertical arrow approximately  $20^\circ$  of deviation to right.

(Dodge & Cline, 1951; Westheimer, 1954a; Ueda & Suzuki, 1965) or in animals (Fig. 8). It is of interest, however, that velocity characteristics of return movements were also found for initial deviations. Initial deviations are tonic movements closely related to the slow phase of nystagmus (Cohen *et al.*, 1964; Suzuki & Cohen, 1966). For example the velocity of initial deviations could equal or surpass that of return movements, quick phases of nystagmus (Fig. 5) or saccades (Fig. 9a-c). In addition the maximum velocity of initial deviations also tended to be linearly related to the amplitude of the movement (Fig. 7 upper graph).

(i) Active return movements were present only in the alert animal and

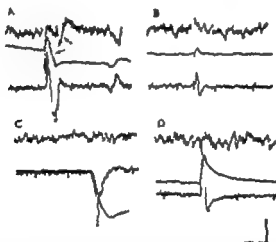


FIG. 11. Evoked potentials of lateral geniculate body of monkey which accompany rapid eye movements in darkness. Top trace of each group is bipolar recording across the dorsal portion of the lateral geniculate body. Second trace is the BC-EOG and third trace is the differentiated EOG. Time base shown by the horizontal bar under D is 100 msec. Vertical bar represents  $20^\circ$  of eye deviation and 100 microvolts. A stimulation of left lateral canal nerve in alert monkey. Return movement is followed by an evoked potential in the lateral geniculate body. Both are shown by arrows. A blink at the end of the trace is also followed by similar evoked potential. B, supillary nerve stimulation in the drowsy animal. C and D given high frequency movements of eyes to left and right.

usually appeared in conjunction with a fast low voltage EEG (Fig 9 a-c). With the first appearance of drowsiness as manifested by a decrease in frequency and amplitude of saccadic movements, slight drooping of the upper lids, and a synchronized EEG both the amplitude and velocity of return movements decreased (Fig 9 f and g Fig 10 B). The time course and appearance of the ocular return in drowsiness suggested that it was probably largely passive. Neither the amplitude nor velocity of initial deviations was much affected in initial stages of drowsiness (Fig. 9 f and g Fig 10 B). However as animals went into deeper sleep or under barbiturate anesthesia the amplitude and velocity of initial deviations was also decreased (Fig 10 C). Ampullary nerve stimuli at this time frequently induced eye deviations which lasted for hundreds of milliseconds. Saccadic movements and the quick phase of nystagmus are also differentially sensitive to decreased alertness. During drowsiness they may be markedly attenuated while slow movements or tonic deviations persist unchanged.

(5) Each rapid movement of the eyes is associated with a potential in the lateral geniculate body in the dark (Feldman & Bender 1960 Cohen, 1965). A geniculate potential accompanying a blink is shown at the end of the top trace of Fig 11 A. Similar potentials were also evoked by lateral canal nerve stimulation when return movements were induced (Fig 11 A, arrows). Lateral geniculate body potentials do not occur during pursuit movements or the slow phase of nystagmus. They were not induced by semicircular canal nerve stimulation in the drowsy state if a return eye movement was not induced (Fig 11 B). Lateral geniculate body potentials also do not occur during rapid passive deflections of the eyes (Fig 11 C and D).

## DISCUSSION

Differences between pursuit and saccadic movements or the slow and fast phases of nystagmus have been apparent since the original studies of Dodge (1903). During pursuit movements and the slow phase of nystagmus vision is present, the angular velocity of the eyes approximates the velocity of the target (Henriksson 1955 Rashbass, 1961) and adjustments in angular velocity are continuous (Rashbass, 1961 Fender & Nye 1961 Stark, Vossius & Young, 1962 Robinson 1965). During saccadic movements or the quick phase of nystagmus on the other hand, vision and the pupillary light reflex are suppressed (Volkman 1902 Zuber Stark & Lorber 1966 Zuber & Stark, 1966) the velocity of the movement is related to the distance the eye has to travel (Dodge & Cline 1901 Ueda & Suzuki 1965) and the movements are beyond voluntary control once they have begun (Westheimer 1954 b Rashbass, 1961). Other differences include those of latency duration and sensitivity to barbiturates (Rashbass & Russell 1961 Robinson, 1965). On the basis of these differences Rashbass (1961) proposed that pursuit and saccadic eye movements are generated differently.



Dodge originally described compensatory movements of the eyes which oppose head movements (1903). He noted that these compensatory eye movements had no measurable latency, were characteristically smooth and slow and were uncontaminated by movements of the type exemplified by saccades (1921). From our data it is apparent that return eye movements are different from the smooth compensatory movements which he described. Instead they are similar to saccades or the quick phase of nystagmus. If Hashbani's supposition is correct then all of these eye movements are probably generated by the same neural organization or mechanisms which are different from those which produce initial deviations, pursuit movements or the slow phase of nystagmus. Study of return movements may therefore lead to further insights into the way rapid eye movements are initiated or modulated. For example it has been shown in this study that velocity is not a true differentiating characteristic between initial deviations and return movements. This implies that tonic deviations or pursuit movements of equal rapidity could have been induced by natural stimuli which were capable of generating a highly coordinated input to the oculomotor system.

A number of factors have been shown to affect the triggering and amplitude of return eye movements. Perhaps most striking is the effect of eye position on initial deviations and return eye movements. This establishes a clear effect of eye position on succeeding eye movements. Changes in the amplitude of nystagmus due to changes in eye position are well known clinically but are usually considered to be a manifestation of Alexander's law that is, due to the unequal elasticity of the eye muscles when the eyes are deviated toward or away from the direction of the slow phase (Carmichael *et al.* 1966). However return eye movements are an active reflex phenomenon and any effect of eye position must have been neural in origin.

The question of how this eye position is sensed is of interest. We have shown that neither passive deflection of the eyes (Fig. 11 C and D) nor VI nerve stimulation will initiate active return movements (Fig. 8 A of Cohen *et al.* 1967). Hence it seems likely that eye position information which initiated triggering of return movements was probably derived largely from internal monitors of the excitatory signal. We would infer that feedback from muscle afferents was relatively unimportant in this respect. Brindley & Milton (1960) have previously demonstrated that there is little conscious eye position sense.

The data also show that the sense of head position summates with that of eye position in initiating return movements. These findings agree with previous studies which show that nystagmus may be produced by changes in the position of the head on the neck which do not stimulate the otolith organ (de Kleijn, 1921; Philipsson, 1962). This emphasizes the important interaction which takes place between head and eye movements in the normal state. This interaction is usually disturbed in studies of pursuit or

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saccadic movements by immobilizing the head. Consequently there is little information on the effect of head movements on the saccadic system. Recently Atkin has shown that rather precise summation of head and eye movements occurs during natural gaze shifts (1964).

Very little is known about the trigger mechanism for either saccades or the quick phase of nystagmus, much less for return eye movements. However several characteristics of the trigger mechanism for return movements can be inferred from the data.

(1) Return movements were recorded at shortest latency (30 msec) only when vision was present. At least 3-5 msec of this 30 msec latency must have been used to couple the eyes to the motor nerve activity (Cohen, Suzuki & Bender 1964). The remainder 25 msec or less, is then the true central latency of the reflex. Since 25 msec is probably shorter than the minimum time it takes for information entering the retina to get to the calcarine cortex and back to the oculomotor nuclei of the brainstem (Cobb & Dawson 1960) visual pathways outside the geniculostriate system must have been responsible for early initiation of the response in the light. Pathways from the retina to the superior colliculus and pretectum are well known (Polyak, 1957). Since the latency from the retina to the superior colliculus is even longer than that of the geniculocalcarine system, it is likely that activity triggering return movements was carried in the other major retinal brainstem projection pathway i.e. the accessory optic tract system. Marg specifically noted in 1964 that units in the accessory optic tract could be activated with a latency of 20 msec. Recently Pasik have concluded that the accessory optic system is the critical structure for preservation of visual perception and optokinetic nystagmus in monkeys after bilateral occipital lobectomy (1966 and personal communication).

(2) The sensitivity of the system generating the quick phase of nystagmus to changes in the level of alertness is known from the studies of Collins (1962), Collins & Guedry (1962) and Crampton & Schwann (1961). The same is probably true for saccadic movements as well (Fig. 9). Operationally we would agree with Collins (1962) that excluding barbiturates (Bergman *et al.* 1952; Rashbass & Russell, 1961) or deep sleep (Dement, 1964) the frequency and velocity of rapid eye movements are among the most sensitive indices of the level of alertness of any including the EEG. Here the finding that very rapid initial deviations can be induced during drowsiness although active return movements do not occur is of interest. It shows that rapid eye movements themselves are not blocked by drowsiness. Instead probably the trigger mechanism for these movements is affected. The same may also be true for saccadic movements and the quick phase of nystagmus.

#### ACKNOWLEDGMENT

We should like to thank Mr. Edward Murray for technical assistance.

## ZUSAMMENFASSUNG

Die elektrische Reizung der Ampullenerven bewirkt bei sich im wachen Zustand befindenden Katzen und Affen entgegengesetzte Bewegungen. Diese bestehen aus einer Bewegung, die das Auge auf den Originalpunkt oder daran vorbeiführt. Die zweite Bewegung wird als „Return movement“ bezeichnet und ist ein zentraler okulomotorischer Reflex. Dieser Reflex kann die Kopfbewegung verbessern, die durch Angularbeschleunigung desselben moduliert wird. Modulierende Einflüsse dieses Reflexes werden durch Sehvermögen, Bewegungen der Augen, des Kopfes und Nuckens und durch den Wachheitszustand des Tieres erklärt. Es besteht eine wechselseitige Beziehung zwischen der Amplitude der eintreffenden Abweichung und der Zurückkehr der Sicht, welche Variationen und Wechsel in der Position der Augen aufweisen. Die Charakteristiken des „Return movement“ sind mit Sakadierung und Rack Nyctagmus verbunden und unterscheiden sich von anderen Augenbewegungen, welche früher beschrieben wurden.

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## EXPERIMENTAL STUDIES ON OPTOKINETIC NYSTAGMUS

### *II Normal Humans*

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This study is an assessment of the functioning of the oculomotor neural reflex in humans. Optokinetic stimuli have been applied by rotating large drums with white stripes on the wall at different velocities around the subjects and the nystagmic movements were recorded electronystagmographically. In the first group of 18 subjects the responses varied both in frequency and amplitude. However there seemed to be two general patterns. One pattern showed a tendency toward small amplitude and high frequency nystagmus and the second pattern small frequency and large amplitude nystagmus. In the second group of 32 subjects two tests were made. During the first test the subjects were instructed to follow the stripes, and in the second they were straight ahead. By following the specific instructions, two different sets of optokinetic nystagmus responses were obtained that corresponded to the two patterns observed in the Group I experiments. Whether "stare" or "look" type responses of the individuals showed a similarity to each other as indicated by the quantitative measurements of the different parameters of the nystagmus. Analysis of the responses showed that the test has a physiological basis and may be of experimental and clinical value.

Previous experiments in cats have demonstrated that an increase in the velocity of the optokinetic stimulus results in a change in the various parameters of the optokinetic nystagmus (i.e. amplitude, velocity of the slow component, duration of the fast and slow phases and frequency). The relationship between the stimulus and the changes in the various parameters of the nystagmus was significantly constant. By precise control of the stimulus it was possible to make quantitative estimates of the functional integrity of the optokinetic reflex mechanism (Honrubia *et al.*, 1967). After these initial observations in cats attention was directed to the study of the same problem in humans. As in the previous experiments, the optokinetic nystagmus was evaluated by electronystagmographic methods. Care was taken to provide optokinetic stimuli at various velocities and with small increments of magnitude. This insured a more precise estimation of

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the relationship between the elicited optokinetic nystagmus and the strength of the stimulus than hitherto has been established (Ehlers, 1926 Gruttner 1939 Mackensen 1954 Enoksson 1956)

### METHOD

A group of 51 subjects (19 males and 32 females) most of them students, was tested in this project. To produce optokinetic nystagmus the subjects were seated in an adjustable chair at the center of a cylinder 50 inches in diameter and 50 inches in height. The bottom of the cylinder was located 24 inches from the floor. Head fixation was achieved by having the subjects resting their chins on a platform which placed their eyes in the center of the cylinder. They were instructed not to turn their heads while the drum was rotating. A black cloth formed the wall of the cylinder and 12 white stripes one degree wide were equally spaced vertically on the wall. The velocity of the drum was controlled by a motor with an adjustable speed system. The drum was surrounded by black curtains which provided isolation from the experimenter and recording apparatus. Diffuse illumination was provided through a white lucite top.

The variation of the corneo-retinal potential produced by the movement of the eyes during the nystagmic beat was picked up from two standard silver chloride skin electrodes placed on the outer canthus of each eye. The ground reference electrode was attached to the subject's forehead. By means of a Grass 7P1 d.c. preamplifier the potentials were differentially recorded and displayed on the chart of the polygraph. The magnitude of the change of the corneo-retinal potential produced by a given angular deflection of the eyes varies from subject to subject depending on among other factors, the location of the electrodes with reference to the orbits. The mean value of the voltage recorded for one degree of deflection of the eyes was 16  $\mu$ V. Since the sensitivity of our preamplifiers and graphic recording systems is as good as 1 mm per  $\mu$ V the resolution of our recording system was sufficient for a detailed study of this problem. Direct measurements were made from the actual recordings.

### RESULTS

The initial experiments were performed in 18 subjects who formed Group I. Based on the information obtained from these experiments a second group of 32 subjects was tested which formed Group II. The subjects in the second group were tested with two different methods and the results were described and classified under Subgroup A and Subgroup B.

#### *Group I Optokinetic nystagmus obtained from subjects tested without receiving specific instructions*

This group was composed of 18 subjects. Each subject was placed in side the optokinetic drum and advised that the drum was going to be



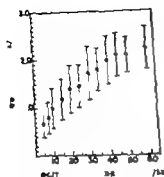


FIG. 1

FIG. 1. Graphical representation of the mean values and standard deviations of the frequency measurement of optokinetic nystagmus elicited at different velocities of the optokinetic drum.

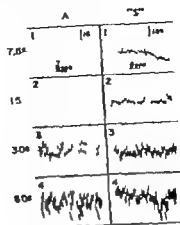


FIG. 2

FIG. 2. Photographs of recordings of the optokinetic nystagmus obtained in two subjects A and S at different velocities of the optokinetic drum.

rotated and they were asked simply to look at the stripes. In each instance the frequency of the elicited optokinetic nystagmus increased with the increase in velocity of the optokinetic drum. The frequency values obtained for any given velocity of stimulus showed large variations from subject to subject. This was evidenced by the standard deviations of the mean values of the frequency measurements (Fig. 1).

The individual behavior of this group of subjects varied, not only with reference to the frequency measurements, but also to the amplitude of the nystagmus. Study of the records of the individual tests showed two distinct patterns of response. One of the patterns was nystagmus of low frequency and large amplitude. The nystagmus of the second pattern was of higher frequency and small amplitude. The nystagmus in each of the 18 subjects followed one or the other of the general patterns. The records of two individuals have been selected to demonstrate the two different types of response (Fig. 2).

The frequency in all instances increased with increased velocity of nystagmus, but the amplitude behavior was distinctly different. Individuals with low frequency curves (Subject A, Fig. 2) showed nystagmus the amplitude of which diminished with increase in frequency. The amplitude of the nystagmus of individuals with large frequency values (Subject S, Fig. 2) became larger as the frequency increased. Figure 3 shows graphically the nystagmus frequency produced at each velocity of the optokinetic stimulus in Subjects A and S. Figure 4 demonstrates the amplitude measurement for both subjects. The values plotted in Figs. 1, 3 and 4 re-



FIG. 3.

FIG. 3 Graphical representation of the mean values of the frequency of the optokinetic nystagmus obtained in subjects "A" and "S"



FIG. 4.

FIG. 4 Graphical representation of the mean values of the amplitude of optokinetic nystagmus obtained in subjects "A" and "S"

the mean values of measurements of the nystagmus during a 30-second test interval

The records indicated that subject A kept his gaze fixed on the wall of the rotating cylinder during the slow phase of nystagmus for longer periods than subject "S". Consequently the nystagmus of subject "A" obtained larger amplitude than that of subject "S". Subject "S" in contradiction performed more nystagmic movements per unit of time than subject A. Although the behavior of the nystagmus for each subject was markedly different at lower velocities of the optokinetic stimulus, the difference was less apparent at higher stimulus velocities. In this group of 18 persons 6 subjects were identified with behavior similar to subject "A". The records of the remaining 12 subjects were more like those of subject "S".

#### Group II Optokinetic nystagmus in subjects after receiving specific instructions

In a second group of 33 subjects the nystagmus was studied under two different conditions. In the first test they were advised to fix their gaze on a stripe and "follow" it with their eyes as far as possible without turning their head. This was designated as the "look" test. In the second test, the subjects were instructed not to follow the stripes but rather to keep their gaze straight ahead. It was emphasized that they must see the stripes passing before them. This was designated as the "stare" test.

#### A Optokinetic Nystagmus Produced by following the Stripes

When the subjects were requested to follow the stripes the nystagmus was of large amplitude (Fig. 5 left Fig. 6 left). The subjects usually picked up a stripe and followed it for about 60°. Some subjects became

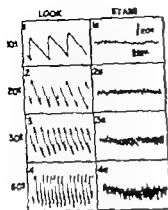


FIG. 5.

FIG. 5. Photographs of recordings of optokinetic nystagmus obtained in one subject of Group II in each of the tests, "look" (left) and "stare" (right).

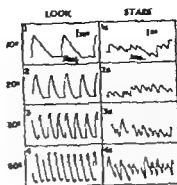


FIG. 6.

FIG. 6. Photograph of recording of optokinetic nystagmus obtained in subject of Group II. The nystagmus during the "stare" test was amplified both vertically and longitudinally (note calibration).

readily engaged in the optic reflex (Fig. 5, left) in which each nystagmic beat was followed immediately by another. In other subjects there was a pause between nystagmic beats (Fig. 6, left). The frequency of the nystagmus increased linearly with increasing velocity of stimulus (Fig. 7 "look").

During these tests the amplitude of the nystagmus remained relatively constant regardless of the velocity of the stimulus.

When the velocity of the stimulus was increased the nystagmic beat becomes double peaked at the end of the quick phase but still big deflections (Fig. 5, left; Fig. 6, left) were produced. The mean values of the amplitude of the nystagmus shown in Fig. 8, "look," are misleading since in the computation of the amplitude all the nystagmic beats both large and small were counted.

#### B Optokinetic Nystagmus Produced by following the Instructions to Stare Straight Forward at the Wall of the Drum

When the same subjects stared at the wall of the drum a completely different nystagmus response was obtained (Fig. 5, right; Fig. 6, right). They performed smaller amplitude movements at much faster rates than previously. The frequency increased with increasing velocity of stimulus (Fig. 7 "stare"). The frequency almost doubled by increasing the velocity from 10 to 40 degrees per second. Further increases in the velocity of the stimulus did not bring a significant increase in the frequency of the nystagmus.

During this test the amplitude of the nystagmus became greater with the increase in the velocity of the stimulus (Fig. 8). The amplitude of the

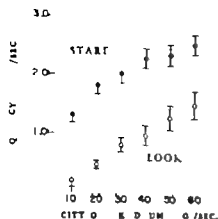


FIG 7



FIG 8

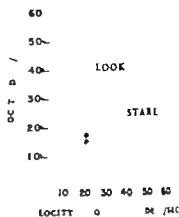


FIG 9

FIG 7 Graphical representation of the mean values and standard deviations of the frequency of the optokinetic nystagmus in both the stare and look tests at various velocities of the optokinetic drum. The results were obtained from all subjects of Group II.

FIG 8 Graphical representation of the mean values of the amplitude of nystagmus obtained at various velocities of the optokinetic drum. The results were obtained from the total 14 subjects tested.

FIG 9 Graphical representation of the mean value of the velocity of the slow component at various velocities of the optokinetic drum.

nystagmus during this test was smaller than that obtained in the previous test at all velocities.

The computation of the velocity of the slow component of the nystagmus during the "stare" test required the use of higher amplification of the signal than was used for the recording of the "look" test. In a group of 6 subjects the stare nystagmus was amplified both vertically and longitudinally to facilitate analysis of the velocity of the slow component (Fig 6, right). The mean value of the measurements made in these subjects at the different velocities of the optokinetic drum are graphically shown in Fig 9. The measurements demonstrated the ability of the subjects to follow the stripes closely at velocities as high as 60 per second during the look test. During the "stare" test the velocity of the slow component showed an increasing lag as the speed of the optokinetic drum was increased.

## DISCUSSION

New information has been obtained which describes the difference between the nystagmus obtained under two different testing conditions. The present work is a continuation and extension of observations made previously by other investigators (Ehlers, 1926; Grutiner, 1930; Mackensen, 1934; and Enoksson, 1956). The use of specific instructions, electronystagmography and precisely controlled optokinetic stimulation has enabled a more precise description of the relationships of the various parameters of nystagmus and the optokinetic stimulus.

It was possible to obtain two distinct patterns of nystagmic responses with physiologically constant characteristics. The nystagmic parameters (frequency, amplitude and velocity of the slow component) are clearly dependent on the strength of the optokinetic stimulus.

Based on experimental work it has been postulated that there are two kinds of optokinetic nystagmus in humans (Ter Braak, 1936; Rademaker & Ter Braak, 1948). These types of nystagmus were called the cortical or "look" nystagmus and subcortical or "stare" nystagmus. This classification was based on whether the cortex participated or was not involved in the nystagmic reflex. There is some evidence however that in man a functional cortex is necessary for the production of the optokinetic nystagmus (Vehrebeuer 1952; Roelofs, 1954).

The subjects in this experiment when under specific instructions to follow the stripes were performing a voluntary movement. If this voluntary motion is considered as nystagmus then this is a cortical nystagmus. Two observations were made which provided some information concerning the underlying mechanisms of the stare test. After performing the "stare" test the subjects were surprised when informed of the frequency of their eye movements. In addition the velocity of the slow component during the stare test behaved similarly to the velocity of the slow component in cats (Honrubia *et al.* 1967). These animals are believed to exhibit only the subcortical "stare" type of nystagmus. Whatever the mechanism of production of the two types of nystagmus (look or stare) may be it appears justified to consider them as two distinct entities.

Precise definition of the optokinetic responses in humans as cortical or subcortical may not be correct. Instructions for obtaining the two different patterns were derived from the observation of the responses from the first group of subjects. These individuals were not subjected to any indication of what was expected from them and their responses must therefore be considered as spontaneous. In the second group of experiments the two specific sets of instructions were based upon the observed behavior in the first experiment. Under each set of conditions, "look" or "stare" a pattern of responses with a physiological constancy was obtained. The quantitative relationship enables determination of deviations from the normal.

Optokinetic nystagmus has been used successfully as a diagnostic test (Barany 1921; Stenger, 1923; Fox & Holmes, 1926; Cogan & Loeb, 1949; Carmichael, Davis & Hallpike 1954; Enbason, 1956 and Keatenbaum 1957). These tests were not always performed using well standardized methods. Quantitative tests similar to those performed during this investigation can provide new information concerning the optokinetic neural reflex in normal and pathological states.

#### ZUSAMMENFASSUNG

Die Forschung ist eine Einschätzung des Funktionieren des Augenmotorreflexes in Menschen. Optokinetische Reize wurden gewandt und man

eine grosse Trommel, an deren Wand sich weisse Streifen befanden, zu verschiedenen Geschwindigkeiten um das Subjekt drehte und die nystagmischen Bewegungen wurden elektronystagmographisch aufgezeichnet. In der ersten Gruppe von 18 Subjekten waren die Reflexantwortungen verschieden in Häufigkeit und Amplitude. Zwei allgemeine Muster schienen jedoch vorhanden zu sein. Eines der Muster zeigte eine Neigung für Nystagmus von geringer Amplitude und grosser Häufigkeit das andere Muster für Nystagmus von geringer Häufigkeit und grosser Amplitude. In der zweiten Gruppe von 32 Subjekten wurden zwei Proben unternommen. In der ersten Probe wurden die Subjekte angewiesen den Streifen zu folgen und in der zweiten geradeaus zu starren. In der Ausführung der spezifischen Anweisungen wurden zwei verschiedene Reflexantwortungsgruppen des optokinetischen Nystagmus erhalten welche den in der Gruppe 1 Probe beobachteten zwei Mustern entsprachen. Unter den Anweisungen „starren“ wie auch „mitgehen“ zeigten die Individuen eine Ähnlichkeit zueinander wie es durch die quantitativen Messungen des verschiedenen Parameters des Nystagmus hervorgebracht wurde. Die Analyse der Reflexantwortungen zeigte dass die Proben physiologische Beständigkeit haben und von Forschungs- und klinischem Werte sind.

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## LYSOSOMIAL ENZYMES IN THE INNER EARS OF KANAMYCIN TREATED GUINEA PIGS

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The activity of acid phosphatase,  $\alpha$ -acetyl  $\beta$ -glucosaminidase and  $\beta$ -glucuronidase were localized histochemically in 36 guinea pigs injected daily with kanamycin sulfate (250 mg/kg body weight) for 1 to 8 weeks. All three lysosomal enzymes showed essentially the same distribution pattern. Before the well-known microscopic damage developed in the outer hair cells, there was a temporary slight increase in intensity and area of enzyme activity. Afterwards, the histochemical reaction became gradually weaker and finally was negative. The inner hair cells underwent the same changes, but later. Ultimately all hair cells were destroyed by this ascending process. Likewise in the spiral ganglion cells enzyme activities initially increased then markedly diminished. These changes started in the apical turn and descendingly involved also the lower turns. Enzyme activities in the spiral ganglion cells returned to normal after cessation of treatment. It appears that histochemical changes in the ganglion cells are independent of the damage to the organ of Corti and therefore not associated with the well-known secondary changes in the ganglion.

Since Umezawa isolated kanamycin in 1958, this antibiotic has been widely used. Its ototoxicity was discovered soon, and well documented studies pointed to the outer hair cells as the primary site of damage. Although of considerable clinical importance the mechanism by which these cells are affected has been unknown.

The distribution and possible significance of lysosomal enzymes in the normal inner ear has been studied before (Ishii & Balogh, 1966; Ishii *et al* 1967). It is generally accepted that lysosomes are involved in cell injury and necrosis; therefore we assumed that a histochemical study of lysosomal enzyme activity in the inner ear may shed light on the mechanism of kanamycin ototoxicity. This paper reports the histochemical changes in the inner ear of kanamycin-treated guinea pigs.

This study was supported by research Grant NE 04153-05 from the National Institute of Neurological Disorders and Blindness, National Institutes of Health of the United States Public Health Service.

TABLE 1 *Kanamycin treatment*

No. of guinea pigs	Weeks of treatment	Total dose (mg/kg body weight)
4	1	1 500
4	2	3,500
10	3	5,250
4	4	7 000
4	5	8 750
4	6	10,500
9	Controls	—

TABLE 2 *Recovery after kanamycin treatment*

No. of guinea pigs	Time after finishing 6-week-course (10,500 mg/kg body weight), weeks
1	1
1	2
2	3
2	4

## MATERIAL AND METHODS

A total of 40 young adult guinea pigs (weighing 250 to 300 g) were used. All animals showed a good pinna reflex and had no middle ear infection. Intraperitoneal injections of kanamycin sulfate<sup>1</sup> (250 mg/kg body weight) were given daily to 36 animals for 1 to 6 weeks (Table 1). Animals were also killed at various intervals after completion of a 6-week-course of treatment (Table 2). Nine untreated animals served as controls.

All animals were decapitated under light ether anesthesia and the temporal bones were removed and dissected immediately. The tissue blocks were fixed in an ice-cold 4% formal-calcium solution for 24 hours, then decalcified in a buffered EDTA solution for 7 days (Balogh 1965; Ishii & Balogh 1966). Decalcified tissue blocks were frozen on Dry Ice and sectioned at 12  $\mu$  in a cryostat at -20 C. Sections were mounted on clean coverslips, thawed and dried at room temperature for 30 minutes.

The activities of acid phosphatase (Barka & Anderson 1962),  $\beta$  glucuronidase (Hayashi *et al.* 1964) and  $\alpha$ -acetyl- $\beta$ -glucosaminidase (Hayashi 1965) were localized by using the various naphthol AS-BI salts of the corresponding substrates. In all instances, hexazonium pararosanilin was employed as a coupler. Nuclei were counterstained with methyl green. The specificity of the reactions was checked by incubating sections in media from which the substrate was omitted.

Kantrex Injection, Bristol Laboratories, Syracuse, New York.





Fig. 1 (upper basal or sad turn) the organ of Corti of kanamycin-treated guinea pigs. The sites of  $\gamma$ -acetyl- $\beta$ -glucosaminidase activity are red but appear black on the microphotographs. Cells counterstained with methyl green are round and are also dark on the photomicrographs. (a) Normal guinea pig. Enzyme activity was localized in the sub-culicula region of outer hair cell (arrow) and the inner hair cell. Enzyme activity is localized throughout the supranuclear cytoplasm. (b) After 2 weeks of kanamycin treatment enzyme activity in the outer hair cell slightly increased in intensity and was localized larger areas. The nucleus is closer to the top of outer hair cell (1st row) (c) After 3 weeks of treatment enzyme activity became weaker and less sharply localized. (d) After 8 weeks the nuclei of all outer hair cells are missing and enzyme activity was no longer demonstrable. (e) At enzyme activity is seen in the inner hair cell. (f) After 8 weeks the inner hair cell is destroyed. In some instances the inner hair cells are still present and showed increased enzyme activity (arrow). (g) Same as (e) but the inner hair cell is lost.

In some instances, alternate sections were stained with oil red O for lipid or with Nissl stain. Some unstained sections were examined for autofluorescence with Zeiss fluorescence microscope using excitation filters Schott BG 12 (2 and 4 mm) and barrier filter No. 3.



FIG. 3.  $\alpha$ -acetyl  $\beta$ -glucosaminidase activity in the spiral ganglion cell of the basal turn in a normal guinea pig (a) and after 6 weeks treatment with kanamycin (b). No significant differences were recognized.  $\times 610$ .

enzyme activity was seen in any section through Rosenthal's canal. Large azo dye granules were noted in a few normal ganglion cells. One to three weeks after kanamycin treatment there appeared to be more ganglion cells with large granules (Fig. 2b). These granules had no autofluorescence and failed to stain with Nissl's stain or with oil red O. The majority of the ganglion cells, however, showed diminution of enzyme activity. The loss of demonstrable enzyme activity was more striking in the upper turns. After 4 weeks treatment the histochemical reaction was very weak in most ganglion cells (Fig. 2d) and by the end of the 6th week enzyme activity was demonstrable only in a few cells (Fig. 2e). At the same time the ganglion cells of the basal turns frequently appeared normal (Fig. 3a and b). After a full course of treatment, recovery began in 2 weeks and 4 weeks after cessation of treatment enzyme activities returned to normal in all ganglion cells (Fig. 2f).

No significant changes in enzyme activities were recognized in other parts of the cochlea or in the vestibular labyrinth.

## DISCUSSION

In agreement with numerous animal experiments we found that initially kanamycin affects the organ of Corti at the basal turn and later ascendingly damages the hair cells in the upper turns. In the earliest phase of kanamycin toxicity we noticed slightly increased amounts of azo dye deposits in the subcuticular area of outer hair cells. This observation correlates with recent electron microscopic findings in the early phase of kanamycin

ototoxicity Lundquist & Wersall (1966) found the subcuticular lysosomes of the outer hair cells aggregated to form large dense bodies. Probably these alterations account for the slight initial increase in enzyme activity anteceding the well known degenerative processes in the organ of Corti. Secondary changes have been observed in the ganglion cell population (Hawkins, 1959; Nicotelli & Costa, 1960; Catalano *et al.*, 1961; Friedmann & Bird, 1961; Ward & Fernández, 1961; Beck & Krahel 1962; Reddy & Igarashi 1962; Ardouin *et al.* 1963; Farkashidy *et al.* 1963; Degreel 1964; Hawkins & Engström, 1964; Kohonen, 1965; Tanaka 1966). These changes are accompanied by depressed cochlear microphonics and action potential (Hawkins, 1959; Owada, 1962; Tyberghelm 1962; Farkashidy *et al.*, 1963; Degreel, 1964). Human inner ears also show damage to the hair cells and loss of spiral ganglion cells in the basal turn after prolonged kanamycin therapy (Benitez *et al.* 1962; Jørgensen & Schmidt, 1962).

In view of this ascending pattern of damage it was paradoxical that lysosomal enzyme activity in the ganglion cells demonstrated damage of a descending nature. The earliest recognizable change in the spiral ganglion was the appearance of large azo dye granules in the cytoplasm of some cells. These granules began to appear 2 weeks after kanamycin treatment and were most numerous after 3 to 4 weeks. Later stages were characterized by a marked diminution of azo dye deposits in all spiral ganglion cells, although the quality of the remaining dye granules did not change. These histochemical changes in the ganglion cells were reversible after cessation of treatment; enzyme activity returned to normal. Recent electron microscopic observation support our contention that the changes in the ganglion cells of kanamycin treated animals are partly primary and are not due to damage to the organ of Corti. Awataguchi *et al.* (1967) reported abnormalities in various subcellular structures, including the distension and increase of Golgi vesicles. Since these organites are known to be rich in acid hydrolases (DeDuke 1963) abnormalities in their enzyme activities are not unexpected. Similar enzyme histochemical changes have also been produced experimentally in other ganglion cells. For instance transection of motor neurons causes striking increase of lysosomal enzyme activities in various species (Bulke *et al.* 1949; Cerf & Chacko, 1958; Colmant 1959; Barron & Tuncboy 1962 and 1964; Söderholm, 1963; Blank & Orblinblügel 1963 and 1966). In all these experiments, lysosomal enzyme activities tried to increase 3 days after nerve transection and remained elevated about 4 weeks postoperatively. Afterwards, enzyme activities returned to normal. Changes closely resembling our findings were reported by Fisher & Sutherland (1965) who studied the nodose ganglion after transection of the cervical vagus nerve and noticed increased acid phosphatase activity already 2 days postoperatively. Similar to our results, they found that after the initial rise enzyme activity decreased and by the 25th day it was markedly diminished. Thus, it may be assumed that kanamycin similarly damages the neuron and causes non specific changes in the spiral

ganglion cells. Our findings suggest that the histochemical changes in the spiral ganglion are causally unrelated to hair cell damage because they are reversible and of a descending type. On the other hand the changes in the hair cells and the secondary changes in the spiral ganglion cells are irreversible and of an ascending nature.

Kanamycin and several related antibiotics are not only ototoxic, but also nephrotoxic. While morphological changes in kidneys after kanamycin treatment have not been studied, viomycin, a similar polypeptide of low molecular weight, damages renal lysosomes. After viomycin administration the renal tubular epithelium of rats degenerates and later becomes necrotic (Staemmler & Karhoff 1956). The early phase of this process is characterized by marked swelling of lysosomes, followed by their disintegration (Caesar 1965; Klein *et al.* 1965). Concomitantly acid phosphatase activity first increased then diminished in the tubular epithelium (Gössner 1963). Thus the sequence of events in the kidneys appears analogous to that in the spiral ganglion cells after kanamycin treatment. From these observations one cannot draw conclusions on the pathogenic mechanism of kanamycin toxicity, but apparently both renal and cochlear damage involves the lysosomes.

#### ZUSAMMENFASSUNG

Die Aktivität der sauren Phosphatase, Acetyl- $\beta$ -Glukosaminidase und  $\beta$ -Glukuronidase wurde histochemisch in 36 Meeresschweinchen, die während 1 bis 6 Wochen täglich mit Kanamycinsulphat (250 mg/kg Körpergewicht) behandelt worden waren, lokalisiert. Die drei lysosomalen Enzyme zeigten im wesentlichen dasselbe Verteilungsmuster. Bevor sich der allgemein bekannte Schaden in den äußeren Haarzellen entwickelte, erhöhte sich die Intensität der Enzymaktivität vorübergehend etwas. Danach wurde die histochemische Reaktion allmählich schwächer und war schließlich negativ. In den inneren Haarzellen waren dieselben Veränderungen erst bedeutend später zu beobachten, bis alle Haarzellen durch diesen ansteigenden Prozess zerstört waren. In den Zellen der Ganglion spirale nahm die Enzymaktivität ebenfalls anfanglich zu, wurde jedoch bald auffallend schwächer und war nach 4 bis 5 Wochen kaum mehr nachweisbar. Dieser Verlauf begann in der apikalen Windung und betraf absteigend auch die unteren Ganglionzellen. Nach Unterbrechung der Kanamycin-Behandlung kehrte in den Ganglionzellen das normale Verteilungsmuster der Enzyme zurück. Die histochemischen Veränderungen in den Ganglionzellen zeigten eine absteigende Tendenz, scheinen deshalb von denen des Cortischen Organs unabhängig zu sein und sind nicht eine Folge der allgemein bekannten sekundären Degeneration.

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ganglion cells Our findings suggest that the histochemical changes in the spiral ganglion are causally unrelated to hair cell damage because they are reversible and of a descending type On the other hand, the changes in the hair cells and the secondary changes in the spiral ganglion cells are irreversible and of an ascending nature

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## OXIDATIVE ENZYMES IN THE COCHLEA

*In Electron Microscopic and Histochemical Study of Succinic Dehydrogenase and Dihydropyridine Adenine Dinucleotide Diaphorase*

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Recently developed formalin techniques for the electron microscopic localization of SDH and NADH-D revealed details about the way that these enzymes are distributed in the cochlea. The degree of activity that was manifested on light microscopy by each kind of cell correlated with its mitochondrial content. The stria vascularis was very reactive. Supporting cells showed more activity than hair cells. This technique revealed precise localization of activity on the membranes of mitochondria. NADH-D appears to be present in the parallel membrane and cistern system that is arranged longitudinally in hair cells.

Convenient histochemical procedures are now available for study of two localizing oxidative enzymes. Succinic dehydrogenase (SDH) and dihydropyridine adenine dinucleotide diaphorase (NADH-D) formerly known as dihydropyridine nucleotide diaphorase, are two important enzymes in the oxidative pathway of Krebs tricarboxylic acid cycle. Earlier work (Barnett 1958; Sedar & Rosa, 1961; Nakai, 1963) involved localization of enzyme sites with the use of tetrazolium salts which became reduced to colored formazan. Recent reports have demonstrated the advantages of using 2,2',3,3'-tetra-*p*-nitrophenyl-3,3'-(3,3'-dimethoxy-4,4'-biphenylene)-ditetrazolium chloride (TNBT) as a reagent for localization at the electron microscopic level of SDH and NADH-D (Sedar *et al.* 1962; Ross & Tsou, 1963; Sedar & Burde 1963; Ogawa & Barnett, 1963). These enzymes cause deposition of a colored formazan of TNBT tetra-*p*-nitrophenyl formazan (TNF). This formazan is desirable for electron microscopy because it is relatively insoluble in the customary reagents used for dehydration and embedding, it resists the electron beam, and it forms very small particles (Sedar *et al.* 1962).

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## OXIDATIVE ENZYMES IN THE COCHLEA

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Recently developed formazan techniques for the electron microscopic localization of SDH and NADH D revealed details about the way that these enzymes are distributed in the cochlea. The degree of activity that was manifested on light microscopy by each kind of cell correlated with its mitochondrial content. The stria vascularis was very reactive. Supporting cells showed more activity than hair cells. This technique revealed precise localization of activity on the membranes of mitochondria. NADH-D appears to be present in the parallel membrane and cytoplasm that is arranged longitudinally in hair cells.

Convenient histochemical procedures are now available for study of two interesting oxidative enzymes. Succinic dehydrogenase (SDH) and dihydropyridine adenine dinucleotide diaphorase (NADH D) formerly known as dihydronicotinamide nucleotide diaphorase are two important enzymes in the oxidative pathway of Krebs tricarboxylic acid cycle. Earlier work (Barnett 1958 Sedar & Rosa, 1961 Nakai, 1965) involved localization of enzyme sites with the use of tetrazolium salts which became reduced to colored formazan. Recent reports have demonstrated the advantages of using 2,2',3,3'-tetra-*p*-nitrophenyl-3,3'-(3,3'-dimethoxy-4,4'-biphenyl)-di-tetrazolium chloride (TNBT) as a reagent for localization at the electron microscope level of SDH and NADH D (Sedar et al. 1962 Rosa & Tsou, 1963 Sedar & Burde 1965 Ogawa & Barnett, 1965). These enzymes cause deposition of a colored formazan of TNBT tetra-*p*-nitrophenyl formazan (TNF). This formazan is desirable for electron microscopy because it is relatively insoluble in the customary reagents used for dehydration and imbedding, it resists the electron beam, and it forms very small particles (Sedar et al. 1962).

The formazan is a blue granular material that results when hydrogen

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FIG. 1. Organ of Corti. Incubation for SDH activity. Hensen's and Deiters' cells, and the region surrounding inner hair cells show more intense activity than the hair cells. Even the hair cells were faintly stained blue when examined with the microscope (Light micrograph 300).

FIG. 2. Stria vascularis. Incubation for SDH activity. All layers of the stria showed intense staining (Light micrograph 300).

atoms are transferred from supplied substrate to colorless TNBT. When sodium succinate is provided the deposit is related to SDH activity. If dihydrodiphosphopyridine nucleotide is supplied the precipitate indicates the localization of NADH D.

We, like previous investigators have become interested in studying oxidative enzymes in the cochlea because the hair cells have a unique nutritive system. They are not closely related to any vascular structures. The reason for this isolation probably is to reduce acoustic noise that could otherwise interfere with the hair cells. The hair cells are nourished via surrounding cells or fluid.

The cochlear microphonic is the electrical result of hair cells activity and a substantial portion of it is resistant to oxygen deprivation (Misrahy *et al.* 1958). Anaerobic metabolism plays a role of unknown importance to hair cells.

#### MATERIALS AND METHODS

Eighteen guinea pigs, weighing approximately 350 g each were used as the experimental animals.



FIG. 2. Mitochondria of the stria vascularis incubated for SDH. Dark or marginal cell mitochondria show more reaction by the intermediate or light cells. The surface of mitochondrial cristae is the reaction site. (Electron micrograph 100,000 $\times$ .)

The inner ear structure of anesthetized guinea pigs were removed and immediately placed in an appropriate reagent. Much of the bone surrounding the cochlea was dissected away and some of Reissner's membrane, stria vascularis and spiral ligament was torn exposing the whole inner ear structure to the chemicals.

In the preparation of tissue the following procedures were employed  
Substrate solution and control

1 Succinic dehydrogenase (SDH) medium: 3 mg of T-NBT (1 mg/ml), 80 mg of sodium succinate in 10 ml of 0.1 M phosphate buffer (pH 7.5) and 0.44 M sucrose.

2 Dihydropteridine reductase (NADH D) medium: 0.3 ml of 2.0 mg% T-NBT, 0.3 ml of 1% NADH, 1.0 ml of 0.1 M phosphate buffer pH 7.5, 1.4 ml of distilled water, 0.23 g of sucrose.

3 Control media: The following control media were used with the above incubation.

(a) Substrate free medium.

(b) 700 mg sodium malonal was added to the incubation medium.



FIG. 4. Outer hair cell incubated for NADH D. At some sites along the parallel membranes lining hair cells this enzyme was present (arrows). (Electron micrograph: 30,000 $\times$ )

FIG. 5. Higher magnification showing the fine granular deposit which resulted from NADH D staining in the hair cell. (Electron micrograph: 100,000 $\times$ )

FIG. 6. NADH D activity in hair cell mitochondria under high magnification. The deposition of formazan on the mitochondrial membrane is well shown. (Electron micrograph: 95,000 $\times$ )

### PROCEDURES

1. The specimens were fixed in cold 0.5% hydroxyadipaldehyde or 4% formaldehyde with 8% sucrose in 0.1 M cacodylate buffer pH 7.6 for 30 minutes. After this prefixation the tissue was washed in several changes of 0.1 M cold cacodylate buffer pH 7.6 containing 8% sucrose for 2 hours. Then the material was incubated in the mixture designed for the demonstrating of SDH and NADH D activity for 20–30 minutes at room temperature.

2. Without any prefixation the specimen was washed in cold 3% sucrose in 0.1 M phosphate buffer pH 7.6 for 15 minutes and incubated in the mixture described above for 20–30 minutes at room temperature.



FIG. 1. Distribution of mitochondria in organ of Corti. Deiter cell has relatively large number of mitochondria (*M*). (Electron micrograph  $\times 8,000$ .)

FIG. 2. Mitochondria of the stria vascularis. Of the three kinds of stria of the cochlea, the stria has the highest content of mitochondria. (Electron micrograph  $\times 8,500$ .)

After incubation, the specimen was washed in cold 8% sucrose briefly and was then fixed in 1% cold osmium tetroxide, dehydrated through graded alcohols and propylene oxide and embedded in Epon plastic. Thin sections were made by an LKB Ultratome and mounted on formvar-coated copper grids. All sections were examined without any additional staining in an RCA EMU 3G electron microscope. A Zeiss photomicroscope was used for study of free-hand sections.

Some specimens have been incubated in control media for 30 minutes in every experiment to rule out nonspecific reaction.

## RESULTS

The staining of each type of cell could be correlated with its mitochondrial content. The more mitochondria a cell had, the more intense the staining as seen with light microscopy. This would be expected, since most activity appeared on the cristae of mitochondria when examined with the electron microscope.



FIG. 4. Outer hair cell incubated for NADH D. At some sites along the parallel membranes lining hair cells this enzyme was present (arrows). (Electron micrograph: 30,000.)

FIG. 5. High magnification showing the fine granular deposit which resulted from NADH D staining in the hair cell interna. (Electron micrograph: 100,000.)

FIG. 6. NADH D activity in hair cell mitochondria under high magnification. The deposits of formazan on the mitochondrial membranes are well shown. (Electron micrograph:  $\times 95,000$ .)

### PROCEDURES

1. The specimens were fixed in cold 0.2% hydroxyaldehyde or 4% formaldehyde with 8% sucrose in 0.1 M cacodylate buffer pH 7.0 for 30 minutes. After this pre-fixation the tissue was washed in several changes of 0.1 M cold cacodylate buffer pH 7.0 containing 8% sucrose for 2 hours. Then the material was incubated in the mixture designed for the demonstration of SDH and NADH D activity for 20-30 minutes at room temperature.

2. Without any pre-fixation the specimen was washed in cold 8% sucrose in 0.1 M phosphate buffer pH 7.0 for 15 minutes and incubated in the mixture described above for 20-30 minutes at room temperature.



FIG. 10. Control incubation with formaldehyde perfusion. No mitochondrial staining occurred but some deposit occurred in the endoplasmic reticulum when the tissue was treated with formaldehyde prior to incubation. (Electron micrograph  $\times 100,000$ )

NADH D activity is exhibited by portions of this membrane system. The reaction products are distributed in a patchy fashion (Figs. 4 and 5). Mitochondrial activity is completely inhibited if formaldehyde is used as a perfusion fixative but endoplasmic reticulum staining withstands formaldehyde (Fig. 10).

#### DISCUSSION

Improved histochemical technique for these two oxidatively reacting enzymes, SDH and NADH D, have simplified the problem of describing their distribution within the cochlea. Light microscopy reveals that the stria vascularis and Deiter's cell are more reactive than hair cells. When their mito-

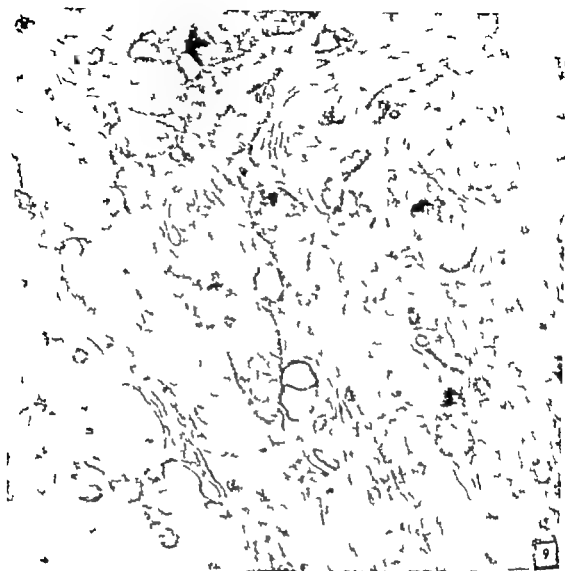


FIG. 9. Control incubation with substrate tri-acularis.  $\lambda$  staining is evident. Dense bodies are evident in many of the mitochondria, but no precipitate formed. (Electron micrograph 60,000)

As Figs. 1 and 2 show the cells of the stria vascularis and Deiter's cells have more intense staining than hair cells as seen with the light microscope. The pattern is quite similar for either SDH or NADH D. The hairs of the hair cells often were the site of large aggregates and may be richly supplied with these enzymes. Inner hair cell hairs were more reactive than other structures of the cochlear duct.

Very fine granules appeared on the membranes of mitochondria with this technique. The deposit occurred in a regular pattern on only the outer surface of the cristae (Figs. 3 and 6). The mitochondria had a similar pattern of staining in every type of cochlear cell.

A parallel array of membranes line the sides of hair cells. They are flat cisterns, which may be connected to the endoplasmic reticulum.



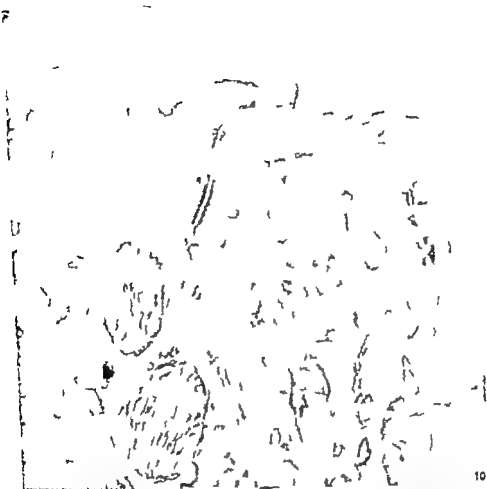


FIG. 10. Control incubation with formaldehyde pre-fixation. A mitochondrial staining occurred but some deposit occurred in the endoplasmic reticulum when the tissue was treated with formaldehyde prior to incubation. (Electron micrograph 100,000 $\times$ .)

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chondrial content is compared by electron microscopy it becomes apparent that the cells with more mitochondria exhibit greater enzyme activity (Figs 7 and 8). Biochemical studies of cellular fractions have showed that most oxidative enzyme activity occurs in mitochondria (Green *et al* 1954; Singer *et al* 1956; Watson & Siekevitz, 1956). No significant difference in staining characteristic emerged in this study between mitochondria from different areas except within the stria vascularis where dark or marginal cell mitochondria were more reactive than intermediate and basal layer cells. This apparent difference may be due to penetration factors.

Nutrition is provided indirectly to hair cells in the organ of Corti. The high rate of oxidative metabolism of the supporting and stria vascularis cells is reflected by their content of mitochondria and these enzymes must be involved in this important role. It may be interesting to speculate about the chemical substances that are received by the hair cells from their surroundings. A great deal of work has been done on the analogous problem of neuron nutrition by glial elements, but the fundamental questions still remain unanswered (Kuffler & Nicolls, 1966). One of the interesting side-lights of these studies regarding the relationship between neuron and supporting cells is the surprisingly high concentration of sodium in the glial cells (Zadunaisky *et al* 1965). In the future we will try to determine whether this same reverse sodium potassium intercellular content is present in cochlear supporting cells.

There is a cistern system of parallel membranes oriented in the long axis of hair cells lining the outer wall along the side of the cells. ATPase activity was not obvious on the hair cell wall in this region (Nakai & Hilding 1967). The cistern membranes do have areas of oxidative enzyme activity as shown in Figs. 4 and 5. In our earlier paper we speculated that the parallel membranes were engaged in transporting substances along the long axis of hair cells. The presence of NADH D on portions of the membrane system may have some importance in its role within hair cells.

## CONCLUSIONS

We used a formazan histochemical technique for studying the distribution of two oxidative enzymes, SDH and NADH D. Generally the relative degree of staining between various types of cochlear cells can be correlated with their mitochondrial content. The more mitochondria cells have the more obvious their staining when they are examined with light microscopy. Within mitochondria, these enzymes are distributed on the outer surface of cristae.

## ZUSAMMENFASSUNG

Jüngst entwickelte Formazan Methoden für die elektronenmikroskopische Lokalisation von SDH und NADH D enthüllten weitere Einzelheiten über die Verteilung

lung dieser Enzyme in der Cochlea. Der Aktivitätsgrad welcher sich in den verschiedenen Zellarten ergibt korrelierte gut mit dem Mitochondriengehalt. Die *Stria vascularis* war sehr reaktiv. Die Stützellen zeigten mehr Aktivität als die Haarzellen. Die Formazanmethode erkennen. NADH D scheint in der Parallelmembran auf der Mitochondrienmembran erkennen. NADH D scheint in der Parallelmembran und im Zytosol, das ist longitudinal in den Haarzellen befindet, vorhanden zu sein.

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Jüngst entwickelte Formazan Methoden für die elektronen mikroskopische Lokalisation von SDH und NADH D enthüllen weitere Einheiten über die Verteilung

### Results

The history questionnaire responses were highly similar to the previously studied normals. However the behavioral effects observed in the present experiment were in general somewhat to considerably less severe in the LDs than in the normals.

No positional alcohol nystagmus was evidenced by any LD subject in either left or right lateral head positions.

To facilitate quantitative comparisons of present results in LD subject with previous results in the normals, the blood alcohol and ataxia test findings in both studies appear as a composite illustration (Fig. 1).

Visual rail walking was the only test on which LDs demonstrated performance decrements following alcohol administration (Fig. 1B). Two hours after ingestion of 80-proof and three hours after ingestion of 100-proof vodka the baseline performance levels were surpassed. In both the 80-proof and 100-proof experiments the LDs were slightly less affected (mean loss of about 2 steps) than the normals (mean loss of 3 to 4 steps).

Although the magnitude of blood alcohol concentration was somewhat higher in LDs than in normals (Fig. 1A) there was a corresponding increase in performance decrements.

Because of the provocative finding of less magnitude and shorter duration of performance decrement in LD subjects than in normals, it was desirable to repeat the experiment using a similar group of LD subjects in an attempt to substantiate and expand on these findings.

### EXPERIMENT II

For better quantitative (numerical) between-group comparison of magnitude effects on alcohol influenced ataxia test behavior three additional bilateral LD subjects, ages 25, 3, and 38, were studied with the following changes in experimental conditions: (1) usual rail walking and usual rail landing tasks were made easier by the use of wider rails to permit equatability of baseline performance scores with those of the normals (but not equatability of baseline vestibular-dependent abilities) and (2) one of the standardized nonvisual tasks performed on the floor—Sharpened Romberg (SR) test, was repeated.

#### Methods

Optimum width of rails for the walking and standing-with-eyes-open task were selected from the standardized Long Version of the rail battery (Graybiel & Freely 1966). These were of sufficient width merely to permit repeatable perfect scores during the morning and afternoon practice sessions held for four days immediately preceding the experimental day. To each individually determined optimum rail were added several succe-

## ACUTE ALCOHOL ATAXIA IN PERSONS WITH LOSS OF LABYRINTHINE FUNCTION<sup>1</sup>

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The effect of alcohol on the postural equilibrium of seven persons with bilateral labyrinthine defects (LDs) was investigated mainly for the purpose of further elucidating the functional role of the vestibular organ in man. Generally, magnitude and duration of the intoxicating effects were found to be less than observed previously in normal persons. The superimposition of an acute alcohol ataxia on persons with pronounced, characteristic vestibular ataxia appears to depend on the degree to which they have compensated for their loss of vestibular function. To the extent that experimental conditions were comparable for both normal and LD subjects the vestibular organ may be regarded as a factor contributing to "acute alcohol ataxia" in normal persons.

Previous reports from this laboratory described a new quantitative ataxia test battery (Fregly & Graybiel 1966; Graybiel & Fregly 1966) and its use in measuring performance decrement in normal persons as a result of alcohol intoxication (Fregly *et al.* 1967). The present report describes the effects of alcohol intoxication on postural equilibrium in two groups of bilateral labyrinthine defective (LD) subjects.

### EXPERIMENT I

#### *Procedure*

#### *Subjects and methods*

The participants were four males, 27, 33, 46 and 50 years of age who with others constitute a comprehensively studied group of LD subjects with nearly if not totally complete absence of vestibular function (Graybiel 1964; Graybiel 1965; Graybiel & Clark 1965; Graybiel & Johnson, 1963; Guedry 1965). All test procedures were identical to those employed previously with normal subjects (Fregly *et al.*, 1967).

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The opinions and conclusions contained in this report are those of the authors and do not necessarily reflect the views and recommendations of the Navy Department.

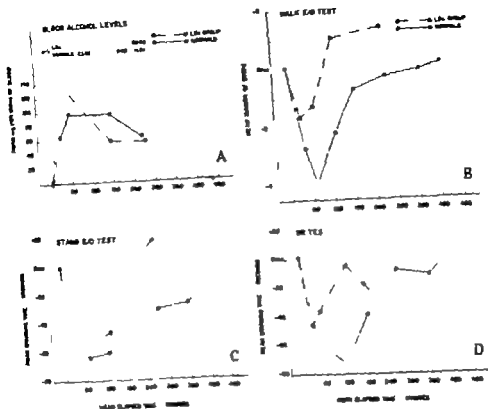


FIG. 2. Comparisons of 100-proof vodka effects in group I (three bilateral labyrinthine-defect subjects (JO, PE, and EA)) with group of thirteen vestibular-normal subjects: (A) Blood alcohol level; (B) rail walking with eyes open; (C) rail standing with eyes open; (D) standing on floor with eyes closed.

The over-all mean baseline performance scores shown in composite Fig. 2 represent the pre-experimental performances of the three LD subjects on their individually tailored rails (mean of 127 Walk Eyes Open steps and mean of 124.8 Stand Eyes Open seconds). Visual rail-walking performance decrements were again observed in the LDs (Fig. 2B). The magnitude of the decrements, the rate at which maximum decrements occurred, and the onset and recovery periods were nearly identical to previous results despite the reduced level of difficulty of the task. In the normals (Figs. 1B and 2B) maximum decrement occurred later (70 minutes after alcohol intake versus 33–45 minutes in the LDs); the magnitude of maximum decrement was greater (mean loss of 4 steps versus a loss of only 2 steps in the LDs) and recovery was later (7 hours versus 2½–3 hours in the LDs) under the influence of the 100 proof vodka.

But unlike the previous LD group, the second LD group showed visual rail-standing decrements; these were remarkably similar to those shown

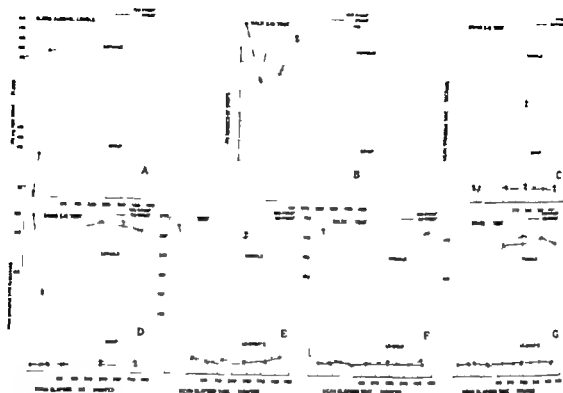


FIG 1 Comparison of 80-proof and 100-proof vodka effects in a group of four bilateral labyrinthine-deficient subjects (DO, GR, HA, MY) with a group of thirteen control normal subjects (A) Blood alcohol level (B) walking with eyes open on 1-inch-wide rail (C) standing with eyes open on 1-inch rail (D) standing with eyes closed on a 2-inch wide rail (E) standing on floor with eyes closed (F-G) standing on floor with eyes closed

sively narrow rails to provide a "top" to each tailor made rail battery. Within group differences in baseline performance scores were thus highly controlled, each subject's baseline score representing a performance near his maximum, but of sufficient difficulty to yield a decrement under the experimental conditions. All subjects also practiced the SR test as often as they did the rail battery.

As before, blood alcohol levels were determined; the drinking history questionnaire was administered and a log of the subjects' behavior was kept. Testing for PAN was not repeated because of negative findings in Experiment I.

### Results

The subjects' accounts of the alcohol effects were limited to physical complaints. The uniform outstanding complaint was that of numbness.

Blood was drawn from the radial artery at the intervals indicated in Experiment I and blood alcohol concentrations were determined by microtechnique using gas chromatography (Colehour 1967).



## DISCUSSION

That decrements in performances by the LD group in Experiment I were observed only on the visual rail-walking task is consistent with the finding that visual rail-walking was the only standardized task which was appreciably compensable for vestibular loss. On the visual rail-standing task and all of the nonvisual (floor and rail) task, the characteristic noncompensable losses shown pre-experimentally in these LDs were far greater than the severity of loss of visual rail walking skill (i.e., performances were initially so poor as to prevent further decrement even with potent alcohol stimulation). The LD subjects' scores on the five tests which were not influenced by alcohol in Experiment I not only were low but also similar (around 10 seconds per test or 3 seconds per trial) the scores made by the normal subjects on the identical tests under control conditions were 80 to 240 seconds per test, or 27 seconds to 80 seconds per trial. The "3-seconds" score seemed to be independent of factors causing differences in performance among normal subjects, and among LD subjects on the partially compensable and, thereby, less vestibular-dependent test—visual rail walking. This minimum, uniform score seemed to be dependent on an initial state of good equilibrium that could be maintained only briefly. If corrective postural mechanisms are called into play to maintain balance for 3 seconds, then our findings indicate alcohol does not influence them. If 3 seconds is too short a period effectively to call postural mechanisms into play, then this represents a (initial) period which is not subject to testing.

On the wider rails and, thereby, "easier tests" employed in Experiment II decrements were observed on both visual tasks. But despite maximization of between-group comparability of decremental effects in terms of better equalizability of baseline scores, decrements in level of performance on visual rail walking skill were again found to be less in LDs than in normals. Smaller decrements in visual rail-standing performances, however, did not obtain. Indeed, these decrements were slightly greater in the LD group than in the normal group. If this result is not attributable to between-group differences in the baseline scores (the test was made somewhat too easy for the LDs and was not nearly as well equated with the normals as was the rail-walking test) and can be shown to be a reproducible finding under conditions of better equalizability of baseline scores with those of normals, it might have theoretical significance in view of the different nature of these two tests. For example, in the LD subjects the standardized Stand Eyes Open task performed on the 2½ inch wide rail is more akin to the standardized nonvisual rail and floor tasks than to the Walk Eyes

The characteristic vestibular ataxia of the LDs is so intense that none was able to meet the minimum criterion for a scoreable trial on the Walk A Line Eyes Closed Test (Frigly & Graybiel, 1968).

TABLE 1 *Influences of 100-proof vodka on the Sharpened Romberg Test performances of the three labyrinthine-defective subjects of Experiment II*

Subject	Baseline score	Individual performances				
		Scores during alcohol stimulation				
		34 <sup>th</sup>	72	134	184	272
JO	18.7	11	1	19	12	18
PE	18.9	14	10	22	33	31
ZA	152.0	32	60	138	93	28

Elapsed time in minutes since 1st alcohol take

by normals although only in terms of magnitude (maximum loss of 10 seconds in the LDs versus 62 seconds in the normals) (Fig 2B). In the normals, maximum decrements in the visual rail standing occurred later (at 70 minutes after alcohol intake versus 33 minutes in the LDs) as did recovery of losses (7 hours versus 2½ hours in the LDs). As with the previous LD group the performances on the visual tasks eventually surpassed the baseline levels.

The alcohol effects on SR performances of two of the subjects, JO and PE (Table 1) were similar in magnitude to the effects seen in the LD subjects of Experiment I (Fig 1E) although relative to the baseline scores the decrement was highly similar to that of the normals (33 per cent in these two LDs versus 31 per cent in the normals). A totally unexpected finding in the exceptional subject ZA was the outstanding improvement of his SR test performance during the practice sessions. Thus the substantially higher SR baseline level of the present LD group (Fig 2D) than of the previous LD group (Fig 1E) was attributable almost entirely to ZA's improved performance. But even subject ZA's baseline level (mean score of 152) was less than the alcohol-depressed SR level in the normals. As was found with the visual rail tasks, maximum SR decrements occurred much sooner than in the normals. Within the LD group subject ZA was least able to maintain his recovery (Table 1). His final score reverted to the level of maximum decrement due to alcohol, but this probably reflected his extreme drowsiness (he slept considerably between testing) in conjunction with a severe headache for which he required aspirin. The SR performances of subjects JO and PE not only regained but surpassed their baseline levels.

The blood alcohol levels of the LDs of Experiment II during the earliest periods of sampling (Fig 2A) were quite similar to those calculated for the LDs of Experiment I (Fig 1A). In the succeeding two periods of sampling the blood levels were more similar to those of the normals.

his counterrolling index is poorer than that of his cohorts (Graybiel, 1964). Thus all other testing of vestibular function to date indicates certain loss of canal function and extreme, if not total loss of otolith function in this subject. On the other hand, ZA was afflicted by meningitis considerably earlier in life than all except one of his cohorts, thus affording him a greater opportunity for nonvestibular proprioceptive sources of compensation for his labyrinthine defect. In addition, he is an individual with outstanding motor coordinative abilities for example he developed ballet skills at an early age. Present experimental findings therefore most likely reflect nonvestibular rather than vestibular origins of his improved SR performance and, thereby the source for the superimposition of an acute alcohol ataxia upon his previous pronounced vestibular ataxia.

The negative positional alcohol nystagmus finding corroborates findings with animals (de Kleyn & Versteegh, 1930) and both earlier results of a different experiment in this laboratory with some of these LD subjects (Harris *et al.*, 1962) and results of experiments elsewhere (Aschan *et al.*, 1956) which attempted to elicit PAN in an analogous group of bilateral labyrinthine-defective individuals. Inasmuch as unilateral vestibular function was found to be sufficient to elicit both phases of PAN (Aschan *et al.* 1964) it would be worthwhile to try to determine the extent to which 1) residual unilateral vestibular function, and 2) residual bilateral function might be sufficient for the elicitation of PAN.

Generally results of Experiment II support the results of Experiment I. Ability to compensate for poor performance skill on a nonvisual task was shown unexpectedly by one LD subject, seemingly due to outstanding utilization of nonvestibular (tactile-kinesthetic) cues in that individual. An additional finding in Experiment II was the disclosure that widening of rails to permit greater opportunity for nonvestibular processes underlying postural equilibrium to operate in the presence of pronounced vestibular ataxia provided, in turn, a greater opportunity to demonstrate the influences of alcohol on such processes.

If it is assumed that the experimental design was adequate, the between-group differences in the alcohol effects on vestibular-dependent ataxia test behavior are accounted for by between-group differences in the integrity of the vestibular apparatus. On the strength of available evidence which argues strongly for overwhelming central nervous system effects of alcohol on behavior and on the assumption specifically that these effects are controlled at the reticular activating system level (Kalant, 1961) then our result may be interpreted simply as follows. In the LD subjects the markedly reduced, if at all functional, vestibular inputs to this central regulatory system were not added to the compound triad of inputs (vision, vestibular function, nonvestibular proprioception) vulnerable to alcohol and required for stringent maintenance of postural equilibrium hence the full effect of alcohol as observed in normal individuals were in a sense, short-circuited.

Open task on the  $\frac{3}{4}$  inch rail, and to the extent that these comparisons in test difficulty levels reflect differences in a) vestibular-dependency and b) nonvestibular sources of compensability for vestibular loss, the differential alcohol effect might well be a reflection of this differential

That improvements over baseline levels were noted in the LDs during both experiments may reflect either additional acquired compensation as a result of the oft repeated experimental testing or a rebound of activity of those structures suppressed by alcohol. Such a rebound has been posited as the explanation of PAN reversal during the hangover period (Kalant, 1961). This pattern was not seen in the normal subjects, even on the task having considerable top in terms of difficulty (visual rail standing). Further investigation is required to determine whether the pattern is specific to LD subjects. Extending the duration of the experiment coupled with the administration of a more difficult visual rail walking task might show similar results in normals.

Since rate and extent of behavioral changes are functions of the rising blood alcohol concentrations (Kalant, 1961) the higher blood levels in the LDs than in the normals in both experiments (Figs. 1A and 2A) would reasonably be expected to reflect more rather than less decrements and slower rather than faster recovery than seen in the normals. The between group differences observed with LDs showing smaller Walk Eyes Open performance decrements in Experiments I and II and more rapid recovery on all three ataxia tests in Experiment II warrant the suggestion that loss of vestibular function lessens the alcohol effects upon the skills studied. This finding may be attributable in part to a superiority of LDs over normals in using nonvestibular cues in difficult walking and standing tests.

Interpretation of the unexpected findings on subject ZA is dependent upon accounting for his startling improvement in SR test performance during the practice sessions. In view of the nonvisual nature of the task such a high degree of compensation necessarily reflects either residual vestibular function a greater ability to compensate through nonvestibular functions than is generally considered possible (Gernandt 1964) or an interaction of residual vestibular function with utilization of nonvestibular cues. Albeit so great a compensation by means of nonvestibular functions alone seems unlikely nevertheless a vestibular source of compensation either residual semicircular canal and/or otolith function, seems more unlikely. ZA has failed repeatedly to show any objective or subjective vestibular responses to brief or sustained rotation (Graybiel 1964 and 1965; Graybiel & Johnson 1963; Guedry 1965) or to intense, sustained ice-water caloric stimulation.<sup>1</sup> Moreover although he is one of the six LDs who have perceived the oculogravic illusion (Graybiel & Clark 1965) he no longer perceived the illusion when tested under water in another experiment (Graybiel *et al.* 1967; Graybiel *et al.* in preparation). Furthermore

Unpublished data, 1966

La durée des effets intoxicants étaient moins dans les personnes normales qu'on avait observés auparavant. La superposition d'une ataxie aiguë d'alcool dans des personnes qui souffrent d'une ataxie caractéristique et prononcée dépend du degré auquel ils ont compensé la perte de la fonction vestibulaire. Comparant tant que possible les conditions des expériences avec des personnes normales et avec des personnes qui ont des déficits bilatéraux du labyrinthe on peut dire que l'organe vestibulaire est un facteur contribuant à l'ataxie aiguë d'alcool dans des personnes normales.

## ZUSAMMENFASSUNG

Die Wirkung von Alkohol auf das Körperliche Gleichgewicht bei Personen mit lateralen Labyrinthdefekten (LD) wurde untersucht, um weitere Aufklärungen über die Rolle des vestibulären Organes im Menschen zu finden. Im Allgemeinen waren Bedeutungen und Dauer der beobachtenden Wirkungen geringer als die die man früher bei normalen Personen beobachtet hatte. Da weitere Hinzufügen einer akuten Alkohol-Ataxie bei Personen mit ausgesprochen charakteristischer vestibulärer Ataxie sich nicht abspielten in welchem Masse sie den Verlust ihrer vestibulären Funktion ausgleichen haben. Soweit die Versuchsbedingungen für normale Personen sowie für solche mit bilateralen Labyrinthdefekten vergleichbar waren, kann das vestibuläre Organ als Faktor angesehen werden, der zu einer akuten Alkohol-Ataxie in normalen Personen beiträgt.

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The further comparison of findings in LDs with previous findings in normals made clear the observation that the visual rail ataxia test items alone are sufficient to demonstrate significant adverse effects of moderate alcohol intoxication whatever the extent to which the performance skills thereon are vestibular-dependent. Thus, consistent with known CNS influences (Gernandt 1964) the alcohol effects on postural equilibrium were basic and generalized rather than specific to the vestibular system. Accountability of the findings in these terms would appear equally valid with respect to the ataxia test differences observed between normals and LDs following prolonged rotation (Fregly & Kennedy 1965) and following a severe storm at sea (Fregly & Graybiel 1965).

Insofar as the between group differences observed in our limited study of the qualitative behavioral changes due to alcohol can be shown to be reliable when studied as stringently as we have studied postural equilibrium then accountability on a vestibular basis, directly or indirectly will have important theoretical implications in view seemingly of the unlikelihood of such accountability.

While alcohol influences on postural equilibrium functioning in our groups of subjects reinforce the important role of the vestibular organ in such functioning, elucidation of the basic role of nonvestibular proprioception during moderate alcohol intoxication although considerably more problematic, requires investigation before the importance or weighting of the vestibular role *per se* in normal persons can become fully known.

### CONCLUSIONS

The findings in this investigation permit the following conclusions:

- 1 The intactness of the vestibular organ may be regarded as a factor contributing to "acute alcohol ataxia" in terms of both the magnitude and duration of the ataxia.
- 2 An "acute alcohol ataxia" is superimposable on a pronounced vestibular ataxia only to an extent, apparently, that such ataxia becomes compensable via nonvestibular processes.
- 3 Qualitative behavioral changes in response to alcohol appear to be of lesser severity and duration in LD subjects than in normal subjects.
- 4 Positional alcohol nystagmus appears nonelicitable in individuals with total or nearly total absence of vestibular function.

### RESUME

Les recherches sur l'effet de l'alcool sur l'équilibre postural des personnes qui ont des défauts bilatéraux du labyrinthe ont pour but la clarification additionnelle de la fonction de l'organ vestibulaire d'homme. En général l'importance et

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### RÉSUMÉ

Les recherches sur l'effet de l'alcool sur l'équilibre postural des personnes qui ont des déficits bilatéraux du labyrinthe ont pour but la clarification additionnelle de la fonction de l'organ vestibulaire d'homme. En général l'importance et



## COCHLEAR PATHOLOGY AFTER DESTRUCTION OF THE ENDOLYMPHATIC SAC IN THE CAT

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The endolymphatic sacs of the left ears of fifteen cats were destroyed surgically and after survival times of six months to three years, twelve were found to have endolymphatic hydrops. Four control ears which were subjected to sham operations and eighteen opposite ears failed to show endolymphatic hydrops. Three of four animals with post peraural survival times of two and half to three years also had trophic changes in the organ of Corti and spiral ganglion which were most severe in the apical regions. Thus it appears that loss of function of the endolymphatic sac not only results in increase in volume of endolymph presumably due to inadequate resorption but also lead to trophy of the sense organ and ganglion of the cochlea. A critical appraisal of all the evidence supports the concept that loss of function of the sac may be the primary etiologic factor in Ménière's disease.

Endolymphatic hydrops has been of interest as a pathological entity since it was first described in 1938 by Hallpike & Cairns as being the principal histological finding in Ménière's disease. Although the hydrops in Ménière's disease usually occurs without other inner ear changes, as in our collection of 8 ears, Lindsay *et al* (1952) recently have found degenerative changes in the organ of Corti and spiral ganglion in two of thirteen ears in their collection. The underlying disorder in Ménière's disease appears to be an imbalance between secretion and resorption of endolymph resulting in an increase in volume of this fluid. On a purely morphological basis most investigators have assumed that the site of secretion of endolymph is the stria vascularis and possibly parts of the cristae, and that the site of resorption of the endolymphatic sac. This has led to a number of experimental attempts to produce hydrops by destroying the sac.

In 1947 Lindsay first attempted to establish a relationship between function of the endolymphatic sac and endolymph volume. He destroyed the sacs of seven monkey ears but failed to find hydrops after survival times of 3 months. In 1954 Lindsay *et al* still not convinced that the endolymphatic sac had no function, performed a similar experiment on cats and

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The endolymphatic sacs of the left ears of fifteen cats were destroyed surgically and after survival times of six months to three years, twelve were found to have endolymphatic hydrops. Four control ears which were subjected to sham operations and eighteen opposite ears failed to show endolymphatic hydrops. Three of four animals with postoperative survival times of two and half to three years also had atrophic changes in the organ of Corti and spiral ganglion which were most severe in the apical regions. Thus it appears that loss of function of the endolymphatic sac not only results in increase in volume of endolymph presumably due to inadequate resorption, but also lead to atrophy of the sense organ and ganglion of the cochlea. A critical appraisal of all the evidence supports the concept that loss of function of the sac may be the primary etiologic factor in Menière's disease.

Endolymphatic hydrops has been of interest as a pathological entity since it was first described in 1938 by Hallpike & Cairns as being the principal histological finding in Menière's disease. Although the hydrops in Menière's disease usually occurs without other inner ear changes, as in our collection of 8 ears, Lindsay *et al.* (1952) recently have found degenerative changes in the organ of Corti and spiral ganglion in two of thirteen ears in their collection. The underlying disorder in Menière's disease appears to be an imbalance between secretion and resorption of endolymph, resulting in an increase in volume of this fluid. On a purely morphological basis most investigators have assumed that the site of secretion of endolymph is the stria vascularis and possibly parts of the cristae, and that the site of resorption is the endolymphatic sac. This has led to a number of experimental attempts to produce hydrops by destroying the sac.

In 1947 Lindsay first attempted to establish a relationship between function of the endolymphatic sac and endolymph volume. He destroyed the sacs of seven monkey ears but failed to find hydrops after survival times of 3 months. In 1952 Lindsay *et al.* still not convinced that the endolymphatic sac had no function, performed a similar experiment on cats and

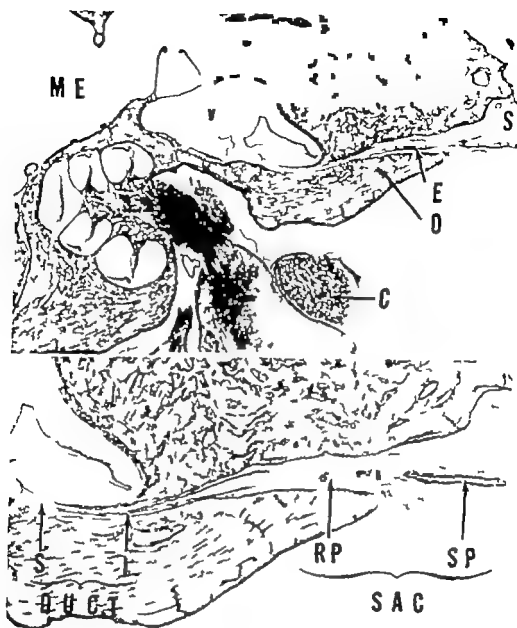


FIG. 1. A diagram of the endolymphatic duct and sac. ME, middle ear; V, vestibular system; S, sigmoid sinus; E, endolymphatic sac; O, oval window; C, choroid plexus. Below S is the isthmus. RP, rugose portion; SP, smooth portion.

again failed to identify endolymphatic hydrops or other pathological changes after survival times of 3 to 9 months.

In an experiment on behaviorally conditioned cats Schuknecht & Kimura (1963) failed to find hydrops or hearing losses after destruction of the endolymphatic sacs and cochlear aqueducts, after survival times of four months and less. Re-examination of the inner ears of these animals, however, reveals mild endolymphatic hydrops in all specimens. The authors had been unwilling to accept this mild hydrops as a significant abnormality because of the lack of control ears.

TABLE 1. Results of surgical destruction of the endolymphatic sac

Postoperative surv. in (mo (year)	No. of animals		Endolymphatic hydrops		Cochlear lesions
	Unsuccessful procedure	Successful procedure	Yes	No	
1		3	3		
1		3	1	2	
1½		3	3		
2	1	2	1	1	
2½	2	1	1		1
3		3	3		2
Operated controls					
2½	4			4	
Opposite ears					
1-3	18			18	1

In 1962, Schuknecht & Seiff reported the findings in two cat ears with survival times of fifteen months following destruction of the endolymphatic sacs. In neither ear was there endolymphatic hydrops. However both showed unexplained atrophy of the organ of Corti and the spiral ganglion in the basal 1 mm of the cochlea. These findings were sufficiently exciting to prompt us to perform a similar experiment with longer survival times. The present report, therefore, is based on an experiment which began in November 1962, and concerns the morphological changes occurring in the inner ears of cats surviving 6 months to 3 years following destruction of the endolymphatic sacs.

In the meantime Kimura & Schuknecht (1963) pursued the hydrops problem in a controlled experiment on guinea pigs with short survival times and for the first time produced hydrops by destroying the endolymphatic sacs.

Even more recently in a report to the American Otological Society Kimura (1967) showed further that in guinea pigs the hydrops is progressive and that degenerative changes occur in the organ of Corti and spiral ganglion, most severely in the apical region in an incidence directly related to survival time.

#### EXPERIMENTAL PROCEDURE

A group of twenty-two healthy adult cats were selected for the study. In eighteen animals the endolymphatic sac of the left ear was destroyed by surgical procedure while the remaining four animals served as controls. The eighteen animals were divided into six groups of three each

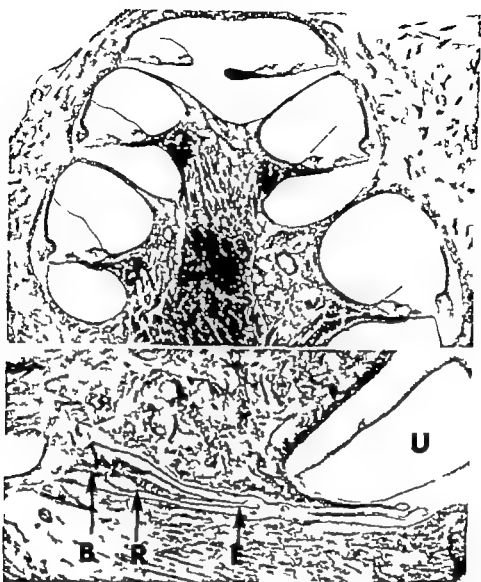


FIG. 2. Above: Absence of endolymphatic hydrop (R is efferent's membrane in normal position) 2 1/2 years after partial destruction of the endolymphatic sac. Below: New bone (B) has replaced part of the sac but at least 30% of the rugose portion (R) remains. The endolymphatic duct (E) and utricle (U) are shown.

with post-operative survival times of 1/2 year, 1 year, 1 1/2 years, 2 years, 2 1/2 years, and 3 years respectively. The four control animals were subjected to a sham surgical procedure without destruction of the endolymphatic sac and all had survival times of 2 1/2 years.

The operative procedure was performed with the animal deeply anesthetized with Pento-barbital Sodium injected intraperitoneally. Utilizing aseptic technique, an occipital craniotomy was performed on the left side. The dura was incised, cerebrospinal fluid aspirated, and the cerebellum was retracted medially. The endolymphatic sac was identified and the operculum (Fig. 1) was drilled away with a 1 mm sharp cutting burr. The

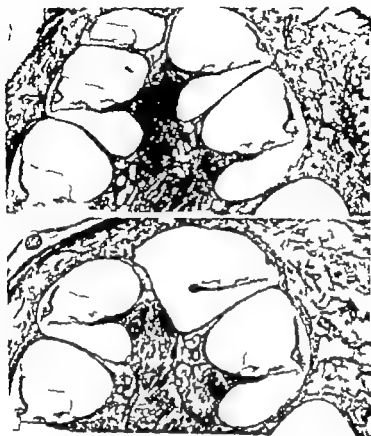


FIG. 2. Above: Mild endolymphatic hydrops 8 months after surgical destruction of the endolymphatic sac. Below: Slightly greater endolymphatic hydrops 1 year after destruction of the sac.

vestibular aqueduct was identified and as much was drilled away as was technically feasible without opening the common crus or vestibule. Gelfoam was placed into the surgical defect, the dorsal margins were approximated, and the scalp incision was closed with catgut suture.

A similar left occipital craniotomy was performed in the control animals. The cerebellum was retracted for a similar period of time and the superior and posterior surfaces of the petrous bone were subjected to a superficial drilling procedure while avoiding injury to the endolymphatic sac. For all twenty-two animals the right ears served as further controls.

The cats were killed by arterial perfusion with Heldenhain-Susa solution while deeply anesthetized with Pento-barbital Sodium. The temporal bones were removed en block with the basis occiput intact and were prepared in anatomical continuity. They were decalcified in Trichloroacetic acid, dehydrated in alcohols, embedded in celloidin, serially sectioned stained with hematoxylin and eosin and mounted on glass slides.



FIG. 4 This ear shows almost total loss of hair cells and spiral ganglion cells in a 6 mm region of the apex 2 1/2 years after destruction of the endolymphatic sac. There also was a 3 mm lesion at the basal end of the cochlea.

## RESULTS

The endolymphatic sacs were successfully destroyed and the specimens prepared without significant artefact in fifteen of the eighteen experimental ears (Table 1). The ears of one animal of the 2 year group had tears of the membranous labyrinth due to improper histologic technique which made assessment of ante mortem pathology unreliable. The surgical procedure was unsuccessful in two of the 2 1/2 year animals. In one of these the posterior semicircular canal and common crus had been inadvertently opened during the operative procedure and in the other the sac was only partly destroyed (Fig. 2).

Endolymphatic hydrops was present in twelve of the fifteen experimental ears in which the endolymphatic sac had been completely destroyed. There was no evidence of endolymphatic hydrops in two of the experimental ears of the 1 year group and one of the experimental ears of the 2 year group. No endolymphatic hydrops could be identified in the opposite ear of any of these animals or in the ears of the four control animals.

The hydrops consisted of mild to moderate displacement of Reissner's membrane towards the scala vestibuli throughout all turns of the cochlea (Fig. 3). The magnitude of displacement was less in the 1-year animals than the 2 year animals but did not progress from the 2nd to the 3rd year.



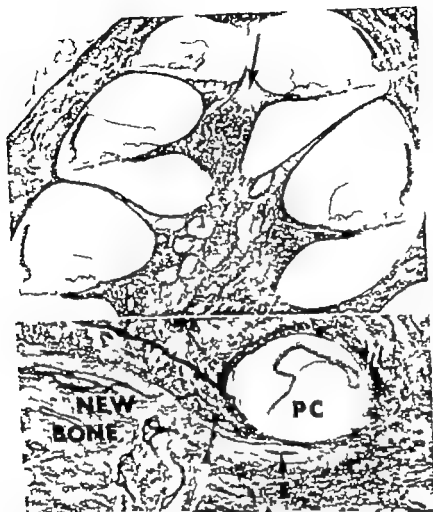


FIG. 5. Histological findings 3 years after destruction of the endolymphatic sac. Above: Moderate endolymphatic hydrops of the cochlear duct and trophy of the spiral ganglion (arrow) in the apical region. Below: The endolymphatic duct (E) is blocked (arrow) by new bone near the posterior semicircular canal (PC).

after surgery. In none of the ears was there distention of the saccule, utricle or semicircular canals.

The organ of Corti and other structures of the cochlear duct, as well as the spiral ganglion, appeared normal in twelve of the fifteen ears in which the endolymphatic sac was successfully destroyed.

In one successfully operated ear of the 2 1/2-year group, there was severe degeneration of both the organ of Corti and spiral ganglion in a 3 mm region of the basal end of the cochlea, as well as in a 6 mm region of the apex, while the intervening portion of the cochlea appeared normal (Fig. 4).

Two of the animals in the 3-year group had cochlear lesions. One con-

sisted of degeneration of the organ of Corti and spiral ganglion in a 5 mm region of the basal end of the cochlea and the other in a 1 mm region of the apex of the cochlea (Fig 5)

Thus it appears that loss of function of the endolymphatic sac not only results in increase in volume of endolymph presumably due to inadequate resorption of fluid but also leads to atrophy of the sense organ and ganglion

There was degeneration of the organ of Corti and spiral ganglion from the 7 to 10 mm region of the unoperated ear of one control animal

### CONCLUSION

The endolymphatic sacs of the left ears of fifteen cats were destroyed surgically and after survival times of 6 months to 3 years and twelve were found to have endolymphatic hydrops. Four control ears which were subjected to sham operations and eighteen opposite ears failed to show endolymphatic hydrops. Three of four animals with post-operative survival times of 2 1/2 to 3 years also had atrophic changes in the organ of Corti and spiral ganglion, which were most severe in the apical regions

The findings are consistent with those of Kimura who has produced both hydrops and cochlear lesions in guinea pigs, following destruction of the endolymphatic sacs

Recent studies by Lindsay *et al* have shown atrophy of the organ of Corti and spiral ganglion in two of thirteen human ears with Menière's disease

Thus it appears that loss of function of the endolymphatic sac not only results in increase in volume of endolymph presumably due to inadequate resorption but also leads to atrophy of the sense organ and ganglion of the cochlea. A critical appraisal of all the evidence supports the concept that loss of function of the sac may be the primary etiologic factor in Menière's disease

### ZUSAMMENFASSUNG

Der Saccus endolymphaticus des linken Ohres wurde in fünfzehn Katzen chirurgisch zerstört. Bei zwölf Tieren wurde nach einer Überlebenszeit von sechs Monaten bis drei Jahren ein endolymphatischer Hydrops festgestellt. Vier Kontrollfälle wie auch die achtzehn gegenseitigen nichtoperierten Ohren zeigten keinen endolymphatischen Hydrops. Drei aus vier Tieren mit einer Überlebenszeit von zweieinhalb und drei Jahren wiesen auch atrophische Veränderungen im Cortischen Organ und Ganglion spirale vor die im apikalen Teil am schwersten waren. Es scheint deswegen dass der Funktionsausfall des Saccus endolymphaticus nicht nur eine Endolymph-Volumenzunahme verursacht was der inadäquaten Resorption zuzuschreiben sein kann sondern auch eine Atrophie des sensorischen Organ und des Ganglion der Cochlea verursachen kann. Eine kritische Auswertung der bisherigen Befunde unterstützt das Konzept dass der Funktionsausfall des Saccus endolymphaticus der primäre etiologische Faktor in Menièr'scher Krankheit sein konnte

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## MONAURAL FREQUENCY DISCRIMINATION IN SUBJECTS WITH MENIÈRE'S DISEASE

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The described technique for measuring DLF gave group mean values on normal subjects comparable to the group mean values of studies by other authors on normal subjects. The group mean values for DLF in subjects with Menière's disease are substantially greater than the same values for normal subjects and the same relationship is true for the standard deviations of the two groups. DLF in Menière's subjects is inversely related to stimulus intensity and shows the greatest separation from normal at the higher frequencies. Pitch discrimination (DL/F) 100 and dispersion of results, (SD F) 100 show the lowest values at 4000 cps for the Menière's group as compared to 2000 cps for the normal group. This, when considered with the tendency for low tone threshold loss, would seem to implicate the upper middle and apical region of the cochlea as the site of greater involvement in Menière's disease. The frequency discrimination studies described in this paper are in no way a clinical test for Menière's disease.

Careful evaluation of the auditory symptoms in patients with Menière's disease frequently calls attention to aberrations of pitch perception both monaural and binaural. Both examiner and patient are more apt to be aware of the "diplacusis binauralis" than they are of the monaural pitch aberration since the latter is somewhat masked by the presence of intensity distortion (recruitment and aural overloading) and changes in timbre of acoustic stimuli.

Extensive research has been done on intensity distortion (the recruitment phenomena) in various types of lesions of the auditory nerve and cochlea in general and in Menière's disease in particular. Relatively few studies have been done on the characteristics of monaural pitch distortion in Menière's disease. Neuman (1951) studied a group of 19 ears with Menière's disease and determined the difference limens for frequency (DIF) at 20 dB in

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lessly above threshold by a frequency modulation technique and compared the results with a group of 23 normal ears. He found consistent differences between the DLF in the normal ears and in the diseased ears at all frequencies (125 cps through 4000 cps) with no overlapping of the ranges at 125, 500 and 1000 cps.

While the frequency modulation or warble technique tests something that is related to the ability of the ear to discriminate frequency the question can be raised as to whether it specifically tests the true difference limen for frequency as pointed out by Harris (1948).

In this study we have chosen a frequency matching technique utilizing two separate stimulus tones separated in time. Many of the published sets of data on frequency discrimination in normal ears have been obtained under pure laboratory conditions where subjects are available for training and repeated testing to insure optimum results from each individual. In this study the subjects with Menière's disease were patients from a busy otology clinic so that economy of time was an important factor. The patient was able to submit to the test procedure on one occasion only. It was anticipated that the data gained in this way would be suitable primarily for comparison of group mean values rather than comparison of the data of an individual of one group with those of another group, since the range of results in untrained individuals would be too great. It is the purpose of this investigation to describe a technique for measuring monaural pitch discrimination suitable for the above-mentioned clinical conditions, to evaluate the results in a group of normal control subjects, to compare the mean values with those of other authors in order to check the validity of our mean values on normal subjects and finally to use this technique in a group of subjects with Menière's disease and evaluate the difference in monaural frequency discrimination ability between the diseased ears and normal ears.

#### *Frequency Discrimination in Normal Ears*

The subject for the study of normal monaural difference limen for frequency were chosen from a group of employees at the Cleveland Clinic. The criteria for selection were normal hearing (at least audiometric 20 dB at all frequencies tested), age (selected to provide representatives of each decade between 20 and 60 years) and intelligence sufficient to understand the test procedure.

The study includes 30 persons, 30 women and 20 men, distributed in the various decades as follows: from 18 through 29 years of age (25 persons), from 30 through 39 years of age (12), from 40 through 49 years (10) and from 50 through 59 years (3). The median age was 28 and the average 32 years.

(1) Intensity values in this paper are expressed according to the ASA scale.

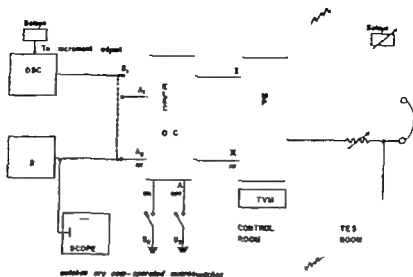


FIG. 1 Block diagram of equipment.

### Description of Equipment

The equipment used for the study (Fig 1) included two General Radio beat frequency oscillators, Model 1304B one variable and one fixed. The variable generator was equipped with two selsyn motors. One selsyn motor was attached to the cycle increment dial of the variable oscillator and was activated by the subject's manipulation of an unmarked dial on the second selsyn motor. The cycle increment dial of the variable tone oscillator was modified so that there was a 300-cycle range on either side of the 0 cps marking. Thus, the subject had a range of 600 cps in which to determine the pitch match. The frequencies from the oscillator were fed into a Grason-Stadler electronic switch with a modification using cam-operated microswitches. The electronic switch then fed the frequency from each oscillator separately at a specified time interval into the amplifier of a Grason-Stadler speech audiometer Model 162 which in turn amplified the frequencies and fed them into the test ear through a telephonic TDH-39-10Z headphone. The interval between the constant tone and the variable tone was 0.25 second; the interval between each pair of tones was one second; and the duration of each tone was one second. The frequency under test was checked by using a Hickok Model 670A oscillograph.

### Description of Test and Test Procedures for Normal Subjects

Each subject was given a pure tone audiometric test in which a Malco Model 1 audiometer was used to determine pure tone thresholds. A General Radio beat frequency oscillator and a Grason-Stadler speech audiometer were used to determine auditory threshold for the test equipment. Frequencies used in difference limen testing were 250, 500, 1000, 2000, and

TABLE 1 Frequency DL—whole sample normal subjects

DL, Difference limen of frequency as measured by the method of constant deviation from the test frequency; s.d., standard deviation of the method of constant deviation; (DL/F) 100—rel. th. DL of frequency in per cent (s.d./F) 100—rel. th. s.d. of frequency in per cent.

Test frequency (cps)	Observation	Intensity above threshold, dB			Average for all intensities
		10	40	80	
200	DL in cps	2.0	1.8	2.0	1.9
	s.d. in cps	1.6	1.5	2.5	1.9
	(DL/F) 100	0.8	0.70	0.80	0.76
	(s.d./F) 100	0.6	0.61	1.00	0.74
500	DL in cps	3.2	3.2	3.5	3.3
	s.d. in cps	2.2	2.1	2.8	2.7
	(DL/F) 100	0.65	0.63	0.70	0.66
	(s.d./F) 100	0.65	0.62	0.55	0.61
1000	DL in cps	4.8	5.2	4.8	4.9
	s.d. in cps	3.1	3.1	4.6	4.3
	(DL/F) 100	0.48	0.51	0.48	0.48
	(s.d./F) 100	0.31	0.31	0.56	0.42
2000	DL in cps	8.9	7.8	7.5	8.2
	s.d. in cps	5.8	4.9	5.3	5.3
	(DL/F) 100	0.45	0.39	0.39	0.41
	(s.d./F) 100	0.29	0.25	0.28	0.27
4000	DL in cps	23.3	18.5	26.6	22.5
	s.d. in cps	20.7	16.3	23.0	21.0
	(DL/F) 100	0.56	0.46	0.66	0.56
	(s.d./F) 100	0.51	0.41	0.57	0.42

4000 cps. Tests of difference limen for frequency were given at the following intensities above each subject's threshold of hearing: 10, 40, and 80 dB. Three matches were recorded in each intensity and a total of nine matches was made for each frequency.

The subject was instructed in the purpose of the test and told that he would hear two tones, one constant and one variable, separated by an interval of silence. He was instructed in the operation of the dial used in controlling the variable tone and asked to match the variable tone with the tone that remained constant. No time limit was placed on the test but each subject was asked to match the two tones as quickly as possible yet still be fully satisfied with his match before stopping. When he was satisfied with his choice he was told to tell the examiner. Monaural difference limen for frequency was recorded by turning the small increment dial of the constant tone oscillator until the oscilloscope matched the frequency of the variable tone oscillator. Initially each subject was given a trial test using 1000 cps at 40 dB above his auditory threshold. This trial lasted until the subject was completely acquainted with the test procedure. After the

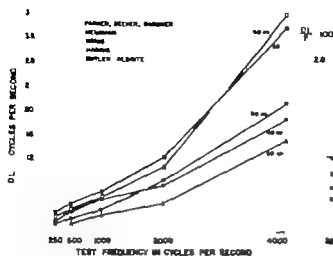


FIG. 2

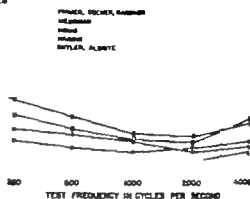


FIG. 3.

FIG. 2 Difference limen as a function of frequency for normal subject compared with those reported by four other investigators.

FIG. 3 The curves of Fig. 2 converted to relative pitch discrimination as indicated by the percentage ratio  $(DL/F) \times 100$ .

trial period the test of monaural difference limen for frequency was started. The sequence for the frequencies tested was as follows: 1000, 2000, 4000, 500, and 250 cps. There was a 10-minute rest period after each one-half hour of testing.

### Statistical Analysis

The following statistics were compiled: the mean deviation of the matches from each test frequency (difference limen for frequency); the standard deviation of each mean deviation; the factor  $(DL/F) \times 100$ ; the factor  $(s.d./F) \times 100$ ; and the significance of difference between the normal ears and the pathologic ears described in the second part of the paper.

The first four statistical computations were also done for intensities of 10, 40, and 80 dB. The formulas used are:

$$\text{Mean } m = \frac{\sum xf}{n}$$

$$\text{Standard deviation } s = \sqrt{\frac{\sum x^2 f}{n} - \left(\frac{\sum xf}{n}\right)^2}$$

$$\text{Significance of difference between two sample means} = \frac{m_1 - m_2}{\sqrt{s_1^2/n_1 + s_2^2/n_2}}$$

### Results in Normal Ears

The results of the DLF studies for the whole sample of normal ears are given in Table 1 for three intensities. The DL for 40 dB is graphically illustrated in Fig. 2 together with the curves reported by four other authors.



TABLE 2. Frequency DL—musically trained and not musically trained subjects at 40 dB intensity

DL, Difference limen of frequency measured by the mean deviation from the test frequency; s.d., standard deviation of the mean deviation (DL/F) 100=relative DL of frequency; percent (s.d./F) 100=relative s.d. of frequency in percent.

Test frequency (cps)	Observation	Musically trained	Non musically trained	Whole sample
250	DL in cps	1.5	2.3	1.8
	s.d. in cps	1.3	2.5	1.5
	(DL/F) 100	0.60	0.92	0.70
	(s.d./F) 100	0.52	1.00	0.60
500	DL in cps	2.6	4.3	3.3
	s.d. in cps	1.9	4.7	3.1
	(DL/F) 100	0.54	0.86	0.62
	(s.d./F) 100	0.38	0.91	0.62
1000	DL in cps	4.7	6.4	5.3
	s.d. in cps	3.4	6.0	5.1
	(DL/F) 100	0.47	0.64	0.51
	(s.d./F) 100	0.34	0.60	0.51
2000	DL in cps	6.7	10.2	7.8
	s.d. in cps	4.2	6.1	4.9
	(DL/F) 100	0.33	0.51	0.39
	(s.d./F) 100	0.21	0.36	0.25
4000	DL in cps	13.6	24.1	18.5
	s.d. in cps	12.9	28.2	19.3
	(DL/F) 100	0.38	0.60	0.46
	(s.d./F) 100	0.32	0.70	0.46

The results compare favorably considering the method and purpose of our technique. The standard deviations for each frequency are considerably larger in our group than those for the other authors. This is to be expected, as mentioned previously because of the absence of training in our subjects. Our results compare favorably enough with those of other investigators to justify the use of mean values gained by the technique for comparison with mean values of groups of pathologic ears.

It is evident from the curves in Fig. 2 that a difference limen for frequency increases steadily as the test frequency is increased and increases precipitously above 2000. This, however, is not a measure of pitch which is the subjects' interpretation of stimulus frequency. Since an interval of a given number of cycles per second does not give the same subjective pitch interval at various points in the audible frequency scale and since equal pitch intervals (octaves) double in cycles per second as we go up the frequency scale, the percentage ratio (DL/F)  $\times$  100, is more closely related to subjective pitch sensation than is the simple difference limen

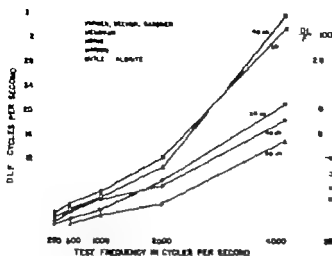


FIG. 2.

FIG. 2 Difference limens for frequency  $f$  for normal subjects compared with those reported by four other in estig ions

FIG. 3 The curves of FIG. 2 converted to relative pitch discrimination  $\Delta f/f$  as indicated by the percent ge ratio  $(DL/f) \times 100$

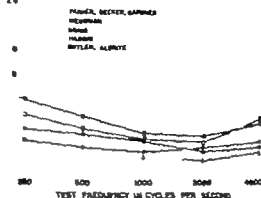


FIG. 3.

trial period the test of monaural difference limen for frequency was started. The sequence for the frequencies tested was as follows: 1000, 2000, 4000, 500, and 200 cps. There was a 10-minute rest period after each one-half hour of testing.

### Statistical Analysis

The following statistics were compiled: the mean deviation of the matches from each test frequency (difference limen for frequency), the standard deviation of each mean deviation, the factor  $(DL/f) \times 100$ , the factor  $(s.d./f) \times 100$ , and the significance of difference between the normal ears and the pathologic ears described in the second part of the paper.

The first four statistical computations were also done for intensities of 10, 40, and 80 dB. The formulas used are:

$$\text{Mean } m = \frac{\sum xf}{n}$$

$$\text{Standard deviation } s = \sqrt{\frac{\sum x^2 f}{n} - \left(\frac{\sum xf}{n}\right)^2}$$

Significance of difference between two sample means

$$\frac{m_1 - m_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

### Results in Normal Ears

The results of the DLF studies for the whole sample of normal ears are given in Table 1 for three intensities. The DL for 40 dB is graphically illustrated in Fig. 2 together with the curves reported by four other authors.

TABLE 2. Frequency DL—musically trained and not musically trained subjects at 40 dB intensity

DL, Difference limen of frequency measured by the mean deviation from the test frequency; s.d., standard deviation of the mean deviation (DL/F) 100—relative DL (frequency in per cent (s.d./F) 100—relative s.d. of frequency in per cent.

Test frequency (cps)	Observation	Musically trained	Non musically trained	Whole sample
250	DL in cps	1.5	2.3	1.8
	s. d. in cps	1.3	2.5	1.8
	(DL/F) 100	0.60	0.92	0.6
	(s.d./F) 100	0.52	1.00	0.60
500	DL in cps	2.8	4.3	3.3
	s.d. in cps	1.9	4.7	3.1
	(DL/F) 100	0.56	0.56	0.62
	(s.d./F) 100	0.38	0.94	0.62
1000	DL in cps	4.7	6.4	5.2
	s.d. in cps	3.4	8.0	5.1
	(DL/F) 100	0.47	0.64	0.51
	(s.d./F) 100	0.34	0.80	0.51
2000	DL in cps	8.7	10.2	7.8
	s. d. in cps	4.3	6.2	4.9
	(DL/F) 100	0.33	0.51	0.39
	(s.d./F) 100	0.21	0.26	0.25
4000	DL in cps	16.6	24.1	18.5
	s.d. in cps	12.9	28.2	19.3
	(DL/F) 100	0.34	0.60	0.44
	(s. /F) 100	0.32	0.70	0.48

The results compare favorably considering the method and purpose of our technique. The standard deviations for each frequency are considerably larger in our group than those for the other authors. This is to be expected as mentioned previously because of the absence of training in our subjects. Our results compare favorably enough with those of other investigators to justify the use of mean values gained by the technique for comparison with mean values of groups of pathologic ears.

It is evident from the curves in Fig. 2 that a difference limen for frequency increases steadily as the test frequency is increased and increases precipitously above 2000. This, however, is not a measure of pitch which is the subjective interpretation of stimulus frequency. Since an interval of a given number of cycles per second does not give the same subjective pitch interval at various points in the audible frequency scale, and since equal pitch intervals (octaves) double in cycles per second as we go up the frequency scale the percentage ratio (DL/F) 100 is more closely related to subjective pitch sensation than is the simple difference limen

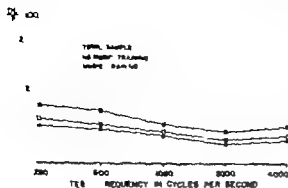


FIG. 4

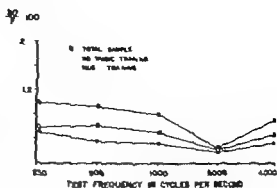


FIG. 5

Fig. 4 Relative pitch discrimination curves for the entire sample compared with musically trained and musically naive groups (40 dB intensity)

Fig. 5 Relative dispersion of the DLF for the normal subjects (total sample, musically trained group and musically naive group) as measured by  $(s.d./F) \times 100$  dB intensity

for frequency. The four curves in Fig. 2 are expressed as this ratio in Fig. 3. These curves indicate that actual subjective pitch discrimination is most accurate in the area of 1000 and 2000 cps.

Statistical analysis of the results of different intensities (10, 40 and 80 dB) did not show any consistent differences at the various frequencies for the three groups with our testing technique. The normal group was divided into two subgroups: those subjects who had musical training or orientation and those who had no musical training or interests. The data for these two subgroups (tested at 40 dB intensity) are given in Table 2 and the factor  $(DI/F) \times 100$  is plotted against test frequency in Fig. 4. It is clear from these results that subjects with musical training or background had consistently better frequency and pitch discrimination ability than did those without musical training or background. The relative dispersion,  $(s.d./F) \times 100$  as shown in Fig. 5 is much less for the musical individuals and illustrates, as would be expected, that musical training is an important factor in discrimination ability and accuracy in frequency studies. It is of interest to note in Fig. 5 that the dispersion of results is less for both groups in the area of 2000 cps where pitch discrimination ability was also found to be most accurate according to the results shown in Figs. 3 and 4. This corresponds to the area of greatest sensitivity to stimulus intensity at threshold as indicated in the curves of threshold audibility of Sivian and White (1933).

#### *Monaural Frequency DL in Pathologic Ears*

Subjects for this group consisted of patients with the clinical diagnosis of Menière's disease who were willing to give several hours of time for the necessary testing. The clinical diagnosis was made on the following basis: (1) a history of episodic true vertigo, tinnitus and hearing loss.

TABLE 3. Frequency DL—subjects having Menière's disease

DL = difference limen of frequency as measured by the method of constant deviation from the test frequency; s.d. = standard deviation of the mean deviation ( $DL/F$ ) 100 = rel. li. DL of frequency 1 per cent; (s.d./F) 100 = rel. li. s.d. of frequency 1 per cent.

Test frequency (cps)	Observation	Sensation level above threshold, dB			Average for all latencies
		10	40	80	
250	DL in cps	8.3	7.4	3.3	6.4
	s.d. in cps	14.3	10.5	4.8	9.8
	(DL/F) 100	3.4	2.9	1.3	2.5
	(s.d./F) 100	6.7	4.2	1.9	3.9
500	DL in cps	16.3	21.2	7.8	14.5
	s.d. in cps	28.8	48.2	11.4	39.4
	(DL/F) 100	3.0	4.3	1.4	2.8
	(s.d./F) 100	5.7	9.6	2.3	5.9
1000	DL in cps	18.1	20.3	24.3	21.0
	s.d. in cps	35.4	38.8	49.6	41.3
	(DL/F) 100	1.8	2.1	2.4	2.1
	(s.d./F) 100	3.5	3.9	5.0	4.1
2000	DL in cps	40.5	32.3	26.3	32.1
	s.d. in cps	66.7	82.6	42.6	51.6
	(DL/F) 100	2.0	1.6	1.3	1.6
	(s.d./F) 100	3.3	2.6	2.1	2.7
4000	DL in cps	63.4	64.0	41.3	57.9
	s.d. in cps	83.3	94.1	67.7	82.4
	(DL/F) 100	1.6	1.7	1.1	1.5
	(s.d./F) 100	2.1	2.3	1.7	2.0

usually a fluctuating nature often associated with a sensation of fullness, hyperacusis, and diplacusis (2) objective findings of a perceptive deafness either affecting the low tones primarily or affecting all frequencies from 125 cps to 8000 cps, and recruitment in at least one frequency (usually 1000 cps).

This group 1 made up of 20 patients, 9 women and 11 men, from 22 through 72 years of age averaging 47 years of age. There were three subjects from 20 through 39 years, six from 40 through 49, eight from 50 through 59 and three from 60 through 72 years of age.

#### Equipment and Test Procedures

The equipment used for testing of the patients with Menière's disease was the same as that described for the group having normal ears, and the test procedure was basically the same with the following modification. Instead of conducting the test at intensity levels of 10, 40, and 80 dB above

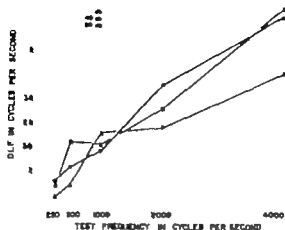


FIG 6

FIG. 6. Difference limen for frequency for three sensation levels above threshold for the ears with Menière's disease (10, 40 and 80 dB).

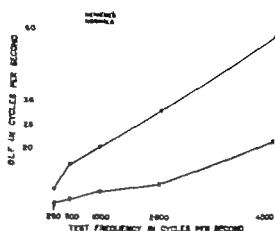


FIG 7

FIG. 7. Comparison of the difference limen for frequency of the Menière group with the normal group, averaging 11 intensities for both groups.

threshold it was conducted at sensation levels of 10, 40 and 80 dB above threshold. Therefore an alternate binaural loudness balance test was conducted in each frequency to find the appropriate sensation level at which to conduct the frequency discrimination test. The test was then conducted in a manner identical to that for the normal group.

## RESULTS

### Intensity relationship

The results for the whole sample of pathologic ears are given in Table 3. Individual curves for the difference limen for frequency at the three sensation levels 10, 40 and 80 dB are presented in Fig. 6. Although the differences between these sensation levels are not consistent at all frequencies, the smallest deviations are found at the 80 dB level in all frequencies but 1000 cps.

This inverse relationship between intensity and frequency discrimination ability in normal ears has been pointed out by previous authors (Schubert, 1957; König, 1957; and others). In this connection it is of interest to note that the best frequency DLs shown in Fig. 2 were those done at the highest intensity level above threshold (90 dB). The presence of this relationship in an ear with Menière's disease is somewhat unexpected in view of the overloading characteristics of the cochlea in this disease as shown by Lawrence & Yantis (1956). In our group of pathologic ears, the 80 dB sensation level at 1000 cps averages 26 dB above threshold. Yet the mean overloading intensity for ears with Menière's disease in Lawrence & Yantis' series for 1000 cps was 13 dB above threshold. Thus, the majority

TABLE 4. Significance of difference between DLF's for normal ears and ears with Menière's disease

Test frequency cps	Confidence level	Z <sup>a</sup>
250	100	3.1
500	100	3.9
1000	100	5.0
2000	100	6.0
4000	100	3.5

100% Confidence level  $Z = 3.00$ .

of ears in our group at 80 dB sensation levels should be overloaded. It might be expected that the presence of aural harmonics would interfere with the DLF and yet, the intensity relationship found in normal ears still holds. Davis and associates (1950) and Schubert (1957) have shown that pitch displacement in noise-damaged ears also decreases with increasing intensity. It, therefore, seems apparent that pitch aberrations in inner ear disease are lessened by increasing intensity.

### Frequency relationships

The DLF's for all intensities averaged together in the pathologic groups are plotted against the same data for the normal group in Fig. 7. It is clear from this graph that there is a substantial difference between the DLF in the two groups at all frequencies. In Fig. 8, the DLF for the

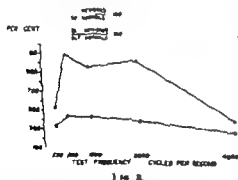


Fig. 8.

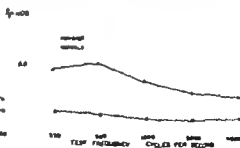


Fig. 9.

Fig. 8 Difference in curves for frequency for the Menière group plotted as percentage of the difference between the normal group and standard deviations of the Menière group plotted as percentage of the standard deviations of the normal group (avg. of all 11 females).

Fig. 9 Retest pitch discrimination curve for Menière group compared with that of the normal group as measured by (DLF) 100 (H intensity) avg.

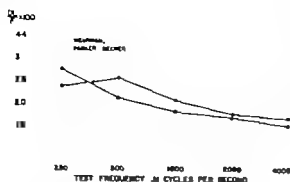


FIG 10

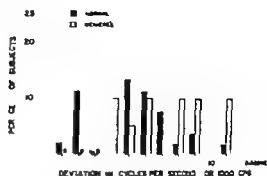


FIG 11

FIG. 10 Relative pitch discrimination curves for the data of the Menière group in this study compared with the same data of Meurman's study measured by  $(DL/F) \times 100$ . (Meurman study 20 dB intensity level above threshold in study a range of 10, 40, and 80 dB sensation level above threshold.)

FIG. 11 Frequency of individual deviation at 1000 cps of the normal group compared with that of the Menière group (a range of all intensities to both groups)

Menière's group is calculated as a percentage between the two  $DL/F$ . Calculation of the significance of difference between the two sample means at each frequency gives a number which falls within 100% confidence level (Table 4). The percentage relationship of the standard deviations of the pathologic group as compared with the normal group is also illustrated in Fig. 8. The extreme difference in this case illustrates well the difficulty and inaccuracy of pitch discrimination in ears with Menière's disease. In Fig. 9 the factor  $(DL/F) \times 100$  is plotted for the normal and abnormal groups. It should be noted that the lowest value for the diseased ear is at 4000 cps, whereas the lowest values in the normal groups are at 2000 cps (Figs. 3, 4, and 5). The percentage difference values in Fig. 8 are also lowest at 4000 and Meurman's (1954) values are also lowest at 4000 for the ears with Menière's disease in his series. Meurman's values agree essentially with ours with minor differences (Fig. 10).

It seems clear from the above data that in Menière's disease the greatest alteration of pitch discrimination ability is in the low tones as measured by the  $DL/F$  and that the accuracy of frequency matching as measured by the standard deviation is relatively worse in the low tones. The smallest difference limens for pitch and the most accurate matching are done at 4000 cps as opposed to 2000 cps for the normal subjects. This greater involvement in the lower part of the frequency range corresponds to the greater loss of threshold sensitivity in the lower frequencies in Menière's disease, particularly in the early and less severe cases.

Schuknecht & Neff (1952) have shown that lesions of the apical and upper middle region of the cochlea produce loss of threshold sensitivity in the low frequency ranges. Tasaki (1954) has shown that nerve fibers from the apex respond to low tones and that fibers from the basilar region



respond to both low and high tones. The correlation of the preceding audiometric data with the localization of function as presented by Schuknecht & Jeff and Tasaki, would seem to implicate the upper middle and apical region of the cochlea as the site of more severe disease in Menière's disease, particularly in early cases.

### Range

In spite of the tremendous difference in mean values between the normal and pathologic groups, the dispersion of individual deviations is such that there is considerable overlapping of the ranges of the two groups so that one cannot predict with accuracy from the data of any individual, whether that individual would have a normal ear or a pathologic ear. The least overlapping in ranges between the DFL for the normal group and that of the Menière group occurs at 1000 cps. This is demonstrated in the bar graph in Fig. 11 where the percentage of subjects having a given deviation is plotted. At this frequency 87% of the deviations for normal are 7 cps and below and 75% of the deviations in the Menière group are 8 cps and above. Thus, in our study any ear with a monaural DFL of 8 cps or above would have approximately an 80% chance of being pathologic.

### ACKNOWLEDGMENTS

The authors wish to express their appreciation to Dr. Earl Schubert and to Dr. Jack Curtis, former of the Cleveland Hearing and Speech Center, Cleveland, Ohio, for their help in modifying the basic equipment to meet the needs of this study and their help in developing the technique used.

### ZUSAMMENFASSUNG

Die hier beschriebene Technik, die DLF von Normalpersonen zu messen, gab Gruppenmittelwerte, die den Gruppenmittelwerten von Normalpersonen anderer Autoren entsprachen. Die Gruppenmittelwerte der DLF von Patienten mit M. Menière waren wesentlich höher als die Gruppenmittelwerte von Normalpersonen der gleichen Bedingungen. Die für die Standardabweichungen in den beiden Gruppen. Die DLF von Patienten mit M. Menière zeigt umgekehrtes Verhalten zu der Reizintensität und hat in den tiefsten Frequenzen die größte Abweichung vom Normalen. Tonunterscheidung (DLF) 100 und Streuung der Ergebnisse (SD) zeigt den Tiefstwert bei einer Frequenz von 1000 in der Menière-Gruppe, verglichen mit einer Frequenz von 1000 in der Normalgruppe. Dies würde das obere Mittelstück und die Spitze der Cochlea bei M. Menière als mehr betroffen erscheinen lassen, wenn man die Tendenz zum Empfindlichkeitsverlust für tiefe Töne nicht acht nimmt. Diese Untersuchungen der Frequenzunterscheidung, die in diesem Artikel beschrieben werden, sind keineswegs ein klinischer Test für M. Menière.

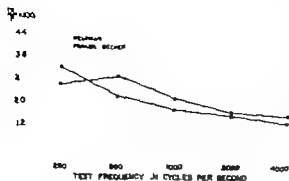


FIG 10

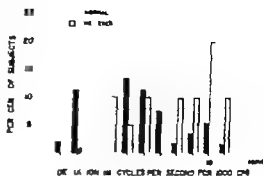


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## EXPERIENCES IN THE TREATMENT OF VASOMOTOR RHINITIS

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Vasomotor rhinitis is the syndrome of a number of allergic and non allergic disturbances on the mucosa of the nose. Consequently before the treatment it is essential to find the real cause and remove or cure it. Our experience specific desensibilization is successful in monovalent sensibility and desensibilization with histamine in certain cases of physical allergy. The component part of our treatment in secondary infection must always be the curing of the sinuses, either by local treatment or conservatively surgical treatment. In some cases the focus in the sinuses may be the source of bacterial allergy. Local treatment of the mucosa of the nose is the component part of our general treatment. Pure vasoconstrictors should be avoided because of the intense reaction. Vasoconstrictors with an antihistamine principle and cortisone should be applied. In cases where our conservative treatment proves unsuccessful, dissection of the vidian nerve either unilaterally or bilaterally should be considered.

The etiology of vasomotor rhinitis being of many different types, the therapy cannot be uniform. We are of the opinion that every case of vasomotor rhinitis should be examined in detail both clinically and in the laboratory in order to be able to apply the appropriate therapy. The component parts of these examinations are the smear of the nose on eosinophiles, an X ray picture of paranasal sinuses, allergic tests, and, according to the history other laboratory and clinical examinations. The testing of eosinophils in the smear of the nose should be performed several times bilaterally. In our experience, eosinophyllia may appear even in non-allergic groups, as a component part of a parasympathicomimetic reaction, but if it is found strongly expressed in addition to the presence of eosinophyllia in the blood, it is more frequently a symptom of allergic reactions. Regarding the intradermal tests on the inhalant allergens and the treatment by desensibilization in allergic vasomotor rhinitis, we cannot give a final and definite opinion. The reasons for this indecision are the following observation. Very often we noticed that, in the course of several intradermal tests, we obtained a different reaction not only according to quantity but also to various allergens. In the course of the treatment we sometimes had evident improvements in the nose although the intradermal reactions remained the same or were even increased. This is why we believe that in the evaluation of cutaneous tests it is necessary to take into consideration

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historical data and the degree of general nonspecific hypersensibility of the patient, which can play an important role in polyvalent sensibility. During the last two years, since we started performing tests and desensibilization in vasomotor rhinitis, 381 patients have been tested, out of which 176 reacted negatively on inhalation allergens. Of 205 patients reacting positively we had fewer cases of univalent and more of polyvalent sensitivity on the first four allergens, as shown in the table.

	Patients			Patients	
House dust	157	Grass pollen		11	
Animal hair	41	Tree pollen		33	
Feathers	77	Moulds		25	
Linen / herbal origin	88	Bacterial vaccine		44	
Linen of animal origin	32	Monilia albicans		9	
		Tobacco		19	

On the basis of our experiences to date with specific desensibilization we offer the following conclusions about this therapy:

- 1 The results are better in monovalent than in polyvalent sensitivity.
- 2 The therapeutic result does not always depend on the strength of the cutane reaction.
- 3 We had the best results in the treatment with house dust and pollen.
- 4 The objective finding in the nose does not correspond to the subjective changes. In an unchanged objective status we have found the normalization of the subjective troubles or the opposite. The cutane tests need not change with the improvement of both subjective and objective signs.

A great problem in vasomotor rhinitis is physical allergy. It is our opinion that such a state does not actually represent an antigen-antibody allergic reaction, but that it is a repercussion of an exaggerated reflexory reaction in the sense of viscerovisceral reflexes whose basis is a neuro-endocrine imbalance. In cases where histamine reaction was very pronounced we applied histamine desensibilization in very small doses over a period of 4 to 6 months and with a certain number of patients we noticed visible improvement. Such improvements were present especially with those patients who had in addition a recurrent oedemata in the face and nose region.

Antihistaminics produce better results in acute allergic cases when the quantity of histamine in the shock organ is greater. The antagonistic effect of antihistaminics is most pronounced on the smooth muscles, a little less pronounced on the reaction of histamine on the blood circulation and hardly visible on the secretion of mucous glands. We came to the conclusion that various kinds of antihistaminics with the same patient can sometimes have a different effect.

The nose and paranasal sinuses are in fact a close whole and there are not any vasomotor reactions on the mucosa of the nose without the same

kind of reactions on the mucosa of the sinuses. Moreover the looser structure of the mucosa of the sinuses makes it possible for the oedema on the mucosa of the sinuses to be more pronounced. Where such conditions last for a long time the blockade of the lymph vessels is possible especially if closing of the ostia of the sinuses appears, which then makes the creation of a secondary infection possible.

In our clinical material we found that nonallergic vasomotor rhinitis is seldom found without this secondary infection of the paranasal sinuses, especially of the maxillary sinuses. Consequently when this fact has been neglected in the therapy of vasomotor rhinitis, there might be created the focus, which not only supports vasomotor reactions of the mucosa of the upper respiratory tract, but can also become a potential source of bacterial allergy.

In a number of patients we obtained satisfactory effects with conservative therapy by applying antibiotics, cortisone and proteolytic enzymes locally on the mucosa of the sinuses. When satisfactory results are not obtained with this therapy the surgical conservative treatment is undertaken. The surgical treatment on allergic and hyperergic areas always represents a potential deterioration of clinical symptoms. That is why such a procedure must be minimal and as much as possible atraumatic, avoiding the removal of the mucosa of the sinuses and creating favourable conditions for drainage and aeration of the sinuses.

In vasomotor rhinitis the operation of the septum is often performed unnecessarily. Only in those cases where even after vasoconstriction of the nasal mucosa, the conductibility of the nose has not been established may we think that the anatomic factor of the deviated septum places a certain rule in the conductivity and the irregularity should be corrected. However in such cases we must also be conservative and remove only that part which causes obstruction.

The use of vasoconstrictors on the mucosa in vasomotor rhinitis, owing to parasympathomimetic reaction very often, after a shorter or longer period of time leads to the opposite reaction, i.e. to vasodilatation and the deterioration of the symptoms of the obstruction of the nose. In order to remove this effect it is necessary to apply vasoconstrictors with antihistamines and cortisone. Very often the question has been put as to how long this local therapy should be applied. In our opinion results cannot be expected from a short treatment but the therapy must be performed for a longer time. This combination does not do any harm to the mucosa and disturbs biochemical balance in the mucosa of the nose, which is very important in such chronic cases. This established balance makes possible an early stoppage of vasomotor attacks, especially in non-allergic cases, in which we can sometimes see that neurovegetative disturbances are spontaneously.

We have had very good experiences with 10 or 15 injections of calcium applied strictly intramuscularly. Its effect is also based on the establish-

ment of biochemical balance in the tissue, the strengthening of the cells membrane and the sympathetic influence. However we are aware of the fact that sometimes even with all these means, we are not able to effect a cure because it is very difficult from a wide syndroma to evaluate the real cause. In such cases we can recommend the dissection of the vidian nerve i.e. the removal of the parasympathicomimetic reaction of the mucosa. Although this method was inaugurated 4 years ago up to now we have operated only 6 cases. This number is small because in most cases we attain success with conservative treatment with medicaments and secondly the patients dislike such operative procedures in vasomotor rhinitis. Last time we pointed out that after such an operation unilaterally the symptoms are often lost bilaterally. We had an opportunity to follow a woman patient who had a relapse after two years, but only on the side where the dissection of the vidian nerve had not been performed. This example speaks in favour of the possibility of a blockade of the parasympathic nerve by the dissection of the vidian nerve in vasomotor rhinitis. Finally we should like to point out that a uniform therapy is not possible where there are syndromes of many diseases. Once again we wish to emphasize that, through anamnestic and clinical findings, the real cause must be found and removed. Vasomotor rhinitis is still a rhinologic problem which is often the consequence of many pathophysiologic conditions of the organism and their repercussion on the mucosa of the nose and the upper respiratory tract.

# ZUSAMMENFASSUNG

Rhinitis vasomotoria ist ein Syndrom allergischer und nichtallergischer Störungen auf der Schleimhaut der Nase. Infolgedessen ist es wichtig vor jeder Therapie den richtigen Grund zu ermitteln um ihn entfernen oder heilen zu können. Nach unserer Erfahrung ist die spezifische Desensibilisation bei monovalenter Empfindlichkeit erfolgreich und unspezifische Desensibilisation mit Histamin in einigen Fällen physischer Allergie. Ein wesentlicher Bestandteil unserer Therapie bei sekundärer Infektion muss immer die Heilung der Paranasalhöhlen sein sei es mittels lokaler Therapie oder durch konservative chirurgische Eingriffe. In einigen Fällen kann diese Infektion eine Quelle bakterieller Allergie sein. Eine lokale Therapie der Nasenschleimhaut ist ein Bestandteil unserer allgemeinen Therapie. Reine Vasokonstriktoren müssen wegen inverser Reaktion vermieden werden. Statt dessen sollten Vasokonstriktoren mit antihistaminischem Prinzip und Cortison angewendet werden. In Fällen wo sich unsere konservative Therapie erfolglos zeigt kommt eine Durchtrennung des Nervus vidianus, sei es einseitig oder beiderseitig, in Betracht.

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## COEXISTING VIRAL (RESPIRATORY SYNCYTIAL) AND BACTERIAL (PNEUMOCOCCUS) OTITIS MEDIA IN CHILDREN

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The occurrence of respiratory syncytial virus and bacteria in otitis media during RS virus infection was studied at a nursery. Middle ear aspirates were cultured for isolation of viruses and bacteria. Antibody responses to the isolated agents were followed. Otitis media was established in 11 of the 13 infected children. RS virus and *Diplococcus pneumoniae* type IV were isolated from the middle ear exudates of 3 children. Both agents were simultaneously present in the exudates of 3 children. RS virus and *Diplococcus pneumoniae* were each isolated from one child. It was not possible to judge from the appearance of the ear drum or from the condition of the exudate the kind of agent present. The etiological relationship between the isolated agent and the observed infection is discussed as well as the value of prophylactic antibiotic treatment.

Otitis media has been found to be common in respiratory syncytial (RS) virus infections (Reilly *et al.*, 1961; Kapikian *et al.*, 1961; Tóth *et al.*, 1965; Berglund *et al.*, 1965 a, 1966 a, b, 1967 a, b). By direct inoculation of middle ear exudates into cell cultures, Berglund and co-workers (Berglund *et al.*, 1966 a, b, 1967 a, b) were able to detect the RS virus in middle ear exudates from infants suffering from acute respiratory infection caused by this agent. In addition to this agent a bacterium (*Haemophilus influenzae*) was cultured from the exudate of one patient (Berglund *et al.*, 1967 a). Because 28 of the 28 subjects studied by Berglund *et al.* had been under treatment with antibiotics at the time of the ear drum puncture, a coexisting bacterial infection could not with certainty be ruled out by negative bacterial cultures in these cases. In the present study additional information was sought on the role of bacteria in the aetiology of otitis media occurring during an RS virus epidemic at a nursery. It was possible to examine the children from the very beginning of their illness and to follow the development of middle ear infection in patients receiving no antibiotic treatment.

This report describes isolation of viruses (RS and adenoviruses) and/or bacterium (*Diplococcus pneumoniae*) from throat swab specimens and middle ear exudates of children with respiratory tract infection accompanying otitis media.

## MATERIAL AND METHODS

The study was carried out in the spring of 1967 during an epidemic of respiratory infection at a nursery unit taking care of 13 children, whose age distribution was as follows

< 3 mo	1
3- 5 mo	3
6-12 mo	5
12-36 mo	3

The conditions prevailing at the nursery have been reported by Berglund & Mäntylä (1966)

Specimens from the throats were taken with swabs and specimens of middle ear exudates by the puncture aspiration technique for viral and bacterial cultures. The techniques are described elsewhere (Lahikainen 1953 Berglund *et al.*, 1966 *a b*) Repeated otological examinations were performed during the course of the illness.

The preparation of cell cultures and the techniques of inoculating and handling these cultures have been reported previously (Berglund *et al.* 1966 *a b* Berglund & Mäntylä 1966 Mäntylä 1966) Identifications of RS virus and adenoviruses were carried out by the methods described by Berglund & Strähmann (1967) and Berglund & Mäntylä (1966) respectively Bacteria were identified as described by Grönroos *et al.* (1964)

Serum specimens were taken for antibody determinations in the acute phase of the illness and on several occasions later the last specimen after 2-6 weeks. The serum specimens were examined for complement fixing (CF) antibodies using the prototype Randall strain of RS virus as antigen and for neutralizing (N) antibodies using one of the isolated strains as antigen as described by Berglund *et al.* (1967 *c*) The sera were also examined for CF antibodies to adenoviruses and haemagglutination inhibition (HI) tests were performed with adenovirus types 1 2 and 5 Antipneumolysin titres were kindly determined by Dr Costa Tuncvall MD Sjukvårdsstyrelsens bakteriologiska centrallaboratorium Stockholm to whom we extend our sincere thanks

## RESULTS

The first case (No. 7) of the epidemic of respiratory infection occurred on February 5th and the second (No. 13) on February 10th Two children (Nos. 1 and 8) became ill 3 days and three (Nos. 6 11 and 12) 4 days after the second child On February 16th four cases (Nos. 2 3 4 and 5) and on the 28th two additional cases (Nos. 9 and 10) were observed According to the clinical signs, the illness in question resembled a respiratory syncytial virus infection This was confirmed by isolation of RS virus from throat specimens. Bronchitis without titis was established clinically in only two

TABLE 1 Isolation of viral and bacterial agents from throat and middle ear exudate specimens and antibody responses to various agents during an epidemic of acute respiratory infection in children at a nursery unit

(+) T = cold rise; RS = respiratory syncytial virus; AD = adenovirus; Pn = *Diplococcus pneumoniae*; Col = coliform; H = haemolytic; CF = complement fixing antibodies; \ = neutralizing antibodies; HI = haemagglutination inhibition; AP = antipneumotysis; — = no signs of illness were observed.

Case no.	Age (months)	Clinical diagnosis	Isolation of infect. agent		Significant rise in antibody titres		
			Throat	Ear	RS	Adeno	Pn
1	10	Bronchitis	RS AD2 Pn	RS Pn	(CF) \	CF + HI by AD5	
2	11	Inf. ac. resp.	RS	RS Pn <sup>b</sup>	CF + \		AP
3	8	Bronchitis	RS	RS H	(CF)		
4	6	Pneumonia	RS	RS <sup>b</sup> Pn	CF + \		AP
5	24	Bronchitis	RS	RS <sup>b</sup>	CF + \		AP
6	9	Inf. ac. resp.	RS AD2 Pn	RS Pn	CF + \	CF (HI by AD2)	
7	11	Bronchitis	RS		CF + \		
8	5	Bronchopneum.	RS	Pn	(CF)		AP
9	4	Bronchiolitis	RS AD2 Pn		(CF) + (N)	CF HI by AD2	
10	1	Bronchitis	RS		—		
11	30	Bronchitis	RS		CF + \		AP
12	12	Bronchitis	RS		CF + \		
13	24	Bronchitis	RS		CF + \		

cases. Six children were found to have bronchitis, one pneumonia, one bronchopneumonia and three bronchiolitis. The features of RS virus infections observed during the earlier outbreak by Berglund *et al.*—nasal discharge, cough, involvement of the lower respiratory tract, and accompanying middle ear infection—were the main manifestations of the illness also during this epidemic.

Four of the children (Nos. 5, 7, 8 and 10) were transferred to three different hospitals. These children could not be followed to the same extent in all respects as the other children; this concerned especially case No. 7.

Four cases (Nos. 2, 3, 11 and 12) were known to have had an RS virus infection during an outbreak 13 months earlier (Berglund & Mäntyjärvi, 1966).

Otitis media was established in 11 of the 13 diseased children. Signs of middle ear inflammation appeared before the second day after the onset of the disease in six cases, before the third day in two, and before the fourth day in one case. The two remaining cases showed signs of middle ear infection on the 10th and 13th day after the onset of the illness. The signs disappeared within 6 to 24 days in seven cases within two weeks or less.

The RS virus was isolated from throat swabs taken from every infant during the first two days of the disease (Tables 1 and 2). Only in three

TABLE 2 *Clinical features of otitis media viral and bacterial isolates*

Date of onset is underlined.

Case	Date	Ear drum	Appearance	Amount of aspirate	Quality of aspirate
1	<u>13.2.</u>				
10 mo	15.2.	1 dx.	Dull, reddened rigid, bulging	++	Turbid mucous
		1 sin.	Dull, reddened rigid, bulging	++	Turbid, mucous
	22.2.	1 a.	Thickened, dull, pale rigid	+	Sticky mucous
	28.2.	1 a.	Normal		
2	<u>16.2.</u>				
24 mo	17.2.	1 dx.	Reddened refl. visible, slightly rigid	+	Turbid, mucous
		1 sin.	Dull, refl. poorly visible slightly rigid	+	Turbid, mucous
	22.2.	1 a.	Thickened, dull, reddened, rigid	+++	Turbid mucous
	28.2.	1 a.	Thickened, dull injected, rigid	+++	Sticky mucous
	6.3.	1 a.	Normal		
3	<u>16.2.</u>				
6 mo	17.2.	1 a.	Thickened, dull rigid	+	Mucous
	20.2.	1 a.	Dull, reddened, rigid bulging	+++	Sticky mucous
	24.2.	1 a.	Thickened dull, slightly reddened, rigid	++	Mucous
	28.	1 dx.	Thickened dull, rigid bulging	+++	Turbid, mucous
		1 sin.	Dull	+	
	6.3.	1 dx.	Normal		
		1 sin.	Slightly injected	±	
	14.3.				
	30.3.				
4	<u>16.2.</u>				
6 mo	17.2.	1 dx.	Dull, slightly reddened rigid, bulging	++	Sticky mucous
		1 sin.	Dull, slightly reddened rigid, bulging	++	Sticky mucous
	20.2.	1 a.	Bulging	++	Sticky turb. mucous
	24.2.	1 dx.	Thickened, dull rigid	+++	Mucous
		1 sin.	Thickened dull, rigid	+++	Mucous
	28.2.	1 a.	Thickened, dull	-	
5	<u>16.2.</u>				
24 mo	17.2.	1 a.	Pale dull, rigid, bulging, small haem rrb.	+++	Sticky turbid mucopurulent
	22.2.	1 a.	Pale thickened slightly reddened rigid, bulging	++	Sticky turb. mucous
	28.2.	1 a.	Slightly injected	+++	Sticky turb. mucous
	6.3.	1 dx.	Dull, rigid	++	Sticky turb. mucous
		1 sin.	Radial injected	++	Sticky turb. mucous
	13.3.	1 a.	Dull	++	Sticky mucous
6	<u>16.2.</u>				
9 mo	17.2.	1 a.	Normal		
	20.	1 dx.	Thickened, dull, slightly reddened	+	Turbid mucous

as well as antibody responses of infants with respiratory infection

NT not tested.

Upper culture		Culture of throat specimens		Antibiotic treatment started	Serum antibody titres				Pa
Viral	Bact.	Viral	Bact.		RS		Adeno		AP
					CF	N	CF	HI	
Rb	—	R9	AD2	NT					
Rb	Pa			15.2. (Peak.)	<4	<4	32	20 (AD5)	100
—	—		AD2	Pa		8	32	20 (AD5)	100
					4	128	2.6	40 (AD5)	200
Rb	—	R5	—		<4	<4	64		50
—	—								
—	Pa	—	—	22.2. (Peak.)		128	64		32
—	—	(inf.)	—			128	32		140
					64	> 128	64		00
—	—	Rb	—		<4	<4	64		2.0
Rb	Pa	Rb	—	20.2. (Peak.)		<4			
	—	—	—			<4	32		50
	—	—	—			4			
					<4	4	128		50
					<4	4			
Rb	Pa	Rb	—		<4	<4	16		70
Rb	Pa	R	—	20.2. (Sample)		<4			
Rb	—	Rb	—		4	16	128		200
					8				
Rb	—	R	—	17.2. (Peak.)	<4	<4	128		0
—	—	—	—				64		
—	—	—	—				128		
					128	128	64		2.0
—	—	—	—			64	128		
		Rb	AD2	NT					
Rb	—	R	—	20.2.	4	<4	64	AD2 128	100
						<4			

Slides stained by Gram method yielded Gram-positive, oval capsule-bearing cocci. The serum antibody titres are given as reciprocals of the serum dilutions. For further abbreviations, see Table 1.

TABLE 2 (Continued)

Case	Date	Ear drum	Appearance	Amount of aspirate	Quality of aspirate
		1 sin	Dull slightly reddened	+	Turbid, mucous
	24.2.	1.a.	Thickened, dull, rigid	++	Turbid, mucous
	28.2.	1.a.	Thickened, dull	+	Sticky mucous
	3.3.	1.a.	Thickened, dull	+	Mucous
	9.3.	1.dx.	Thickened, dull slightly reddened	+	Mucous
		1.sin.	\ normal		
	13.3.	1.a.	\ normal		
7	8				
11 mo	8.2.				
	9.2.	1.a.		+	
	22.2.	1 dx.	Thickened pale dull rigid	+	Fluid, mucous
	2.3.	1 sin.	Thickened, pale dull	+	Fluid, mucous
	8.3.	1.a.	Thickened		
8	13.2.				
5 mo	14.2.				
	24.2.	1.a.	Thinn reddened, refl. visible rigid	+	Sticky mucous
	3.3.	1 dx.	Thinn, dull, rigid	+	Haemorrh., mucous
		1.sin.	Thinn dull	-	
	8.3.	1.a.	\ normal		
	14.3.				
	22.3.				
	6.4.				
9	22.2.				
4 mo	1.3.	1 dx.	Dull, slightly injected	±	Clear serous
		1.sin.	Dull, slightly injected	++	Turbid, mucous
	6.3.	1.a.	Thickened dull, slightly reddened, rigid bulging	+++	Sticky purulent
	13.3.	1 dx.	Slanty discharge		Mucous
		1 sin.	Thinn, slightly rigid radial injected	++	Mucous
	17.3.				
	20.3.	1.a.	Thicken d, dull rigid, injected	+	Mucous
	29.3.	1.a.	\ normal		
	6.4.				
10	22.2.				
1 mo	1.3.	1 dx.	Dull, slightly redd red rigid, bulging	+	Sticky turb. mucous
		1.sin.	Dull, reddened	++	Sticky turb. mucous
	9.3.	1 dx.	Thickened, rigid	+	Sticky mucopurulent
		1 sin.	\ normal		
	13.3.	1.a.	\ normal		
	30.3.				
11	14.2.				
30 mo	15.2.				
	3.3.	1.a.	Thickened radial injected	++	Clear serous
	9.3.	1.a.	\ normal		

Aspirate culture			Culture of throat specimens		Antibiotic treatment started	Serum antibody titres				Pn AP
Viral	Bact		Viral	Bact.		RS		Adeno		
						CF	N	CF	HI	
—	Pn				(Penic.)					
—	—		RS	Pn			< 4			
—	—		—	—			8	128		
—	—		—	—			128			
—	NT		AD2	—		32	8	> 256	AD2 10	100
NT	Str. viridans		RS	HL infl.	S.S. (Ample)	< 4	< 4	4		140
—	—						16	8		280
—	—					64	32	8		140
—	—		RS	NT	S.S. (Penic.)	< 4	< 4	32		50
—	—		RS	—			< 4	32		200
—	Pn		—	—			< 4	32		
						< 4	< 4			
						< 4	< 4	256		200
						< 4	4	32		
—	NT		RS AD2	—	S.S. (Penic. 1 S.S.)	< 4	< 4	< 4	< 10 (AD2)	
—	—									
—	Prod. vir		RS	AD2 Pn			4			
—	—			—			< 4			
			RS AD2	NT	S.S. (T. trac)		< 4	4	10 (AD2)	50
			—	—		4	4	4	10 (AD2)	36
						4	4	8	20 (AD2)	
—	—		RS	—	S.S. (Tetracycl.)	< 4	32	8		280
—	—		—	—			32	4		
						< 4	32	8		70
—	—		RS	NT		4	4	64		100
			—	—	S.S. (Penic.)	64	64	32		0
							64	32		200

TABLE 2 (Continued)

Case	Date	Ear drum	Appearance	Amount of aspirate	Quality of aspirate
12	14.2.				
12 mo	14.2.				
	2.3.				
13	16.2.				
24 mo	14.2.				
	2.3.				
	17.3.				

cases was the RS virus found in throat swabs taken one week after the first successful isolation. In the one case (No 9) in which RS virus was isolated from a throat swab taken on the 17th day after the onset of the illness, a relapse had occurred. *Diplococcus pneumoniae* type XII and adenovirus type 2 were also isolated from the throats of three infants (Nos. 1, 6 and 9).

RS virus was isolated from the middle ear exudates of six children (Nos. 1-6) from 12 specimens in all. RS virus without any accompanying agent was isolated bilaterally from one child (No 5). In three cases (Nos. 2, 4 and 6) in which RS virus was isolated from the middle ear exudates, the virus was simultaneously isolated from the throat specimens. In the other cases it was isolated earlier from the throat specimens.

*Diplococcus pneumoniae* type XII was established in middle ear exudates of six children (Nos. 1-4, 6 and 8) from 13 specimens in all. RS virus and *Diplococcus pneumoniae* type XII were both established in exudates aspirated from six ears (Nos. 1, 3 and 4). In two cases (Nos. 4 and 6) the RS virus was isolated from the exudate from one ear while pneumococcus was isolated from the exudate aspirated from the other ear.

Pneumococcus only was isolated unilaterally from the middle ear exudate of one child (No 8).

In case No 7 who first fell ill *Streptococcus viridans* was isolated from the exudate of the middle ear taken at the hospital. *Proteus mirabilis* was isolated from the exudate of case No 9. It was, however, not detected on staining and hence its presence in the culture was most probably due to contamination.

The middle ear exudate specimens obtained on three different occasions from one of the children were all positive for RS virus. This was the only case in which pneumococcus was also isolated from specimens taken on the first repeated puncture four days after the first puncture. Of the children known to have experienced a re-infection, only one did not exhibit signs of otitis media.



Isolate culture		Culture of throat specimens	Antibiotic treatment started	Serum antibody titres			
				RS		Adeno	
Viral	Bact.	Viral	Bact.	CF	N	CF	HI
		RS	NT	<4	<4	>128	
				64	64	64	
		RS	NT	<4	<4	128	
				128	>128	64	
					64	128	
							70
							100
							100

It has thus been definitely demonstrated that both RS virus and bacteria can be present in middle ear exudates and hence have to be considered as aetiological factors in otitis media occurring during RS virus infections. As only one case of coexisting RS virus and bacterial otitis media has been reported previously, the clinical features, viral and bacterial isolates, as well as the serum antibody responses of our cases are summarized in Table 2.

The signs of middle ear inflammation and the conditions of the exudates are listed in Table 3. Dullness, redness and bulging of the ear drum were the signs most often observed. It was not possible for the examiner to draw any conclusions from the appearance of the ear drum or from the condition of the exudate as to the kind of agent later isolated from the exudate. The signs seemed, however, to be weaker in ears yielding RS virus only than in ears yielding both RS virus and pneumococci.

Continuous accumulation of exudate in the middle ear occurred in one infant (No. 1) with a cleft palate until the adenoids were extirpated. In this case the anatomical circumstances had influenced the course of the middle ear inflammation.

The RS virus infection was verified by a significant rise of CF and/or neutralizing antibody titres in 9 cases. The RS virus CF antibody titres of the acute serum phase were less than 4 in all cases and the neutralizing antibody titres were less than 4 in all but the one infant aged one month (No. 10) in whom the titre was 32. Eight children showed an 8-fold or greater rise in titre and six showed titres of 64 or higher. Only a two-fold rise in CF and/or neutralizing antibody titres occurred in three children, and no increase of antibodies to RS virus occurred in one infant aged 1 month.

Three of five children (Nos. 1, 4, 6, 8 and 9) found positive for adenovirus type 2 developed a 4-fold or greater rise of CF antibodies to adenoviruses. In only two cases (Nos. 6 and 9) was the rise of the HI antibodies

TABLE 2 (Continued)

Case	Date	Ear drum	Appearance	Amount of aspirate	Quality of aspirate
12	11.2.				
12 mo	14.2.				
	2.3.				
13	16.2.				
24 mo	14.2.				
	2.3.				
	17.3.				

cases was the RS virus found in throat swabs taken one week after the first successful isolation. In the one case (No 9) in which RS virus was isolated from a throat swab taken on the 17th day after the onset of the illness, a relapse had occurred. *Diplococcus pneumoniae* type XIV and adenovirus type 2 were also isolated from the throats of three infants (Nos. 1, 6 and 9).

RS virus was isolated from the middle ear exudates of six children (Nos. 1-6) from 12 specimens in all. RS virus without any accompanying agent was isolated bilaterally from one child (No 5). In three cases (Nos. 2, 4 and 6) in which RS virus was isolated from the middle ear exudates, the virus was simultaneously isolated from the throat specimens. In the other cases it was isolated earlier from the throat specimens.

*Diplococcus pneumoniae* type VII was established in middle ear exudates of six children (Nos. 1-4, 6 and 8) from 13 specimens in all. RS virus and *Diplococcus pneumoniae* type VII were both established in exudates aspirated from six ears (Nos. 1, 3 and 4). In two cases (Nos. 4 and 6) the RS virus was isolated from the exudate from one ear while pneumococcus was isolated from the exudate aspirated from the other ear.

Pneumococcus only was isolated unilaterally from the middle ear exudate of one child (No 8).

In case No 7 who first fell ill *Streptococcus viridans* was isolated from the exudate of the middle ear taken at the hospital. *Proteus mirabilis* was isolated from the exudate of case No 9. It was, however, not detected on staining and hence its presence in the culture was most probably due to contamination.

The middle ear exudate specimens obtained on three different occasions from one of the children were all positive for RS virus. This was the only case in which pneumococcus was also isolated from specimens taken on the first repeated puncture four days after the first puncture. Of the children known to have experienced a re-infection only one did not exhibit signs of otitis media.

negative for adenovirus in this study and the rise of HI antibodies for adenovirus type 5 in case No. 1.

Viruses and bacteria can obviously be simultaneously present in middle ear exudates. It cannot in all cases be postulated with certainty to what extent pneumococcus was also aetiologicaly related to the infection of the lower respiratory tract and which of the two agents was the primary cause of the respiratory illnesses. If we take into consideration the two children from whom pneumococcus was not isolated but in whom a significant rise in antipneumolysin titre occurred, there were ten children in all who evidently had contracted a pneumococcal infection in addition to the RS virus infection. The typical clinical finding of RS virus infection in these children indicates that the RS virus most likely was the primary agent and that pneumococcal superinfection had occurred. RS virus infection may have promoted the spread of pneumococcus among the children in the nursery and paved the way for pneumococcal superinfection. On the basis of our own results we do not definitely know in which order these agents invaded the middle ear but it seems that it could have happened simultaneously in some of the children.

The present study provides further evidence of the importance of taking specimens for the isolation of viruses at an early stage of the illness. Attempts to isolate RS virus from throat specimens obtained after the first successful isolation yielded negative results when these specimens were taken 10 days—in most cases 7 days—after the onset of the illness. RS virus could not be isolated from the middle ear exudates later than one week after the first positive puncture and only in one case from specimen taken at repeated punctures.

It is noteworthy that no pneumococci were isolated from children receiving antibiotics at the time of puncture and that no bacterial otitis media developed in two children (Nos. 3 and 10) who were treated with antibiotics from the very onset of the illness. Bacterial middle ear inflammation and most likely also other bacterial superinfections may be prevented by prophylactic treatment with antibiotics in RS virus infection. This prophylactic antibiotic treatment may be of value in respiratory infection as caused by RS virus, especially during institutional RS virus outbreaks and in cases where the infant is exceptionally exposed to contacts.

Only one infant aged 1 month showed no increase in antibodies to RS virus. This is in accordance with the fact that the antibody response to RS virus infection is poor in very young infants. The low antibody titres to RS virus found in case No. 1 may be explained by a too short sampling interval of only two weeks because of the discharge of the infant from the nursery. According to previous experience significant rises in RS virus antibody titres do not occur in infants less than 3 months old before 3 to 4 weeks have elapsed from the onset of the illness (Berglund *et al.* 1965 a).

The low rise in HI antibody response to adenovirus type 5 infection which afflicted infant No. 1 early in January and the absence of antibody

TABLE 3 *Signs of otitis media in and conditions of exudates from ears positive for RS and/or pneumococcus*

	RS	RS + Pn	Pn
Ear drum			
Thin			1
Thickened	2		4
Pale	2		
Dull	3	5	7
Reddened	2	5	4
Haemorrhagic	2		
Bulging	2	6	1
Rigid	4	0	7
Exudate			
Mucous	4	0	7
Mucopurulent	2		
Turbid	4	4	5
Sticky	2	4	1
Sanguinic			1
No of ears	6	6	7

demonstrated with the type isolated from the throat whereas in the remaining three cases HI antibodies to a different type or no HI antibodies were established.

A significant rise in antipneumolysin titre occurred in five children. Pneumococci were isolated from middle ear exudates from three of these children whereas they were not isolated from any specimen from the two remaining children. No rise was observed in 5 further children harbouring pneumococci.

#### DISCUSSION

Two concomitant agents, RS virus and *Diplococcus pneumoniae* type XI had evidently been the causal agents in the epidemic of respiratory illness studied. RS virus is known to spread easily among infants at nurseries with high resultant infection rates (Sternier *et al.*, 1966). In the present study all infants at the nursery unit were involved. It is also known that of pneumococcal infections those caused by *Diplococcus pneumoniae* of type XI are the most prevalent among infants, that the healthy carrier rate of this type is very low and that institutional spread of this type among infants does occur (Finland 1942; Smillie & Jewell 1942). In addition to the two causal agents found, adenovirus type 2 may have contributed to the infection in three cases of the present series. From the beginning of January 1967 adenoviruses 1 and 5 had repeatedly been isolated from several infants showing slight signs of respiratory infection. This well explains the significant rises in adenovirus CF antibody titres in children found

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response to adenovirus type 2 isolated from this infant in the middle of February may be ascribed to retarded antibody production.

As to antipneumolysins, it is known that the antibody response to pneumococcal infection is of low order in young infants (Tunevall 1953). The youngest infant of this series developed no antibodies to pneumolysin. Four of five children in which low antibody response to viral agents were observed failed to produce antibodies to pneumolysin.

Whether RS virus is also associated with the so-called sterile otitis frequently found in older age groups (Grönroos *et al.* 1964) remains an open question. The coexistence of viral and bacterial infection of the middle ear necessitates further virological and bacteriological investigations to elucidate the interactions of both types of agents in middle ear inflammation.

### ZUSAMMENFASSUNG

Das Auftreten von RS-Virus (respiratory syncytial) und Pneumokokken in Mittelohrentzündung wurde während einer RS-Virusepidemie in einem Kleinkinderheim an 13 Kindern untersucht. Zwecks Isolierung von Viren und Bakterien erfolgten Viruszüchtungen aus Mittelohraspiraten. Die den isolierten Krankheitserregern entsprechenden Antikörper wurden beobachtet. Eine Mittelohrentzündung konnte bei 11 der untersuchten 13 Kleinkinder festgestellt werden. Sowohl der RS-Virus als *Diplococcus pneumoniae* Typ XVI wurde aus den Mittelohrexsudaten von 5 Kindern isoliert. Gleichzeitig waren beide Krankheitserreger in den Exsudaten dreier Kinder vorhanden. Bei einem Kind wurde der RS-Virus und desgleichen bei einem Kind *Diplococcus pneumoniae* isoliert. Weder aus dem Aussehen des Trommelfells noch aus der Beschaffenheit des Exsudates konnten hinsichtlich der Art des Krankheitserregers irgendwelche Schlüsse gezogen werden. Zur Diskussion standen sowohl die ätiologischen Beziehungen zwischen den isolierten Krankheitserregern und der beobachteten Infektion einerseits und andererseits die Bedeutung prophylaktischer Behandlung mit Antibiotika.

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exist, as these may indicate central initiation and control of the frequency pattern. In this case the frequency and the amplitude must be regarded as expressions not only of the peripheral stimulus but also of the condition of those areas of the brain stem which are engaged in initiating the fast phases.

A decrease in wakefulness will abolish the fast phase and turn the eyes in the direction of the slow component (Nathanson & Bergman, 1938). With returning wakefulness the fast phase will reappear probably first giving a low frequency. As a consequence an increase in wakefulness may cause an increase in frequency with a corresponding decrease in amplitude. As smoking has been found to increase the alertness, as judged by EEG (Yamamoto & Domino, 1964) a simultaneous change of the nystagmus pattern might be expected. With this background studies of the nystagmus pattern before and after smoking were carried out. In the present work the amplitude and the frequency of the nystagmus beats, the velocity of the slow and fast components, as well as the deviation of the eyes, were compared before and after smoking.

#### METHODS AND MATERIAL

Twenty-one healthy subjects, ten females and eleven males varying in age from 20 to 33 years, were examined. They were classified, according to their smoking habits, into occasional smokers (0-4 cig./day  $n=7$ ), moderate smokers (5-10 cig./day  $n=7$ ) and heavy smokers (11-20 cig./day  $n=7$ ).

##### *Performance of the Test*

The experiments were performed in darkness with the test subject sitting in a rotating device which could be exposed to an angular acceleration of 120 sec<sup>-2</sup> 1.8 sec. The head was free to move in any direction. The subject was instructed to keep the eyes open during the whole test. Each subject was rotated for one minute at three different times before immediately after and fifteen minutes after smoking.

For the smoking part of the test the subject was allowed to smoke a non-filter cigarette (John Sjöström Swedish Tobacco Company) for three minutes. One deep inhalation of smoke was made every fifteen seconds. Immediately after the last inhalation the rotation was started. The test subject had not been allowed to smoke during the previous two hours. After a time-interval varying between 4 to 21 days the test was repeated on each subject.

Before the start of rotation every test subject was calibrated with respect to horizontal eye and head movements of twenty five degrees from the mid-point. The mid-position of the eyes was checked before and after rotation.

## EFFECT OF CIGARETTE SMOKING ON THE VESTIBULAR NYSTAGMUS PATTERN

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Cigarette smoking was shown to give rise to obvious changes of the vestibular nystagmus pattern and these changes were ascribed to central influences. It was demonstrated that the fast phase affected the nystagmus pattern by changing its velocity but above all by changing the time for its interruption of the slow phase. Early interruptions thus increased the frequency and decreased the amplitude. The qualities initiated in the vestibular receptor, the speed of the slow component and the deviations of the eyes in the direction of the fast component, were not significantly changed. Heavy smokers were found to have less changes in the nystagmus pattern by smoking than moderate smokers.

A vestibular nystagmus reaction is made up of a slow and a fast component. The angular velocity of the slow component is found to express very faithfully variations in the vestibular stimulus (Henriksson, 1956) while that of the fast component can be varied by changes within the central nervous system (CNS) (McCabe, 1965).

The frequency and the amplitude have also been used for evaluation of the nystagmus pattern. Their relation to the vestibular stimulus and the velocity of the slow component is however somewhat complex. Torok (1948) has found that the frequency and Mittermaier (1955) that the amplitude to some extent will reflect the vestibular stimulus. However as the product of frequency and amplitude equals more closely the speed of the slow component than either of the two (Ohm, 1939) neither of the factors will be as good a measure of the peripheral stimulus as the speed of the slow component itself.

A variation in frequency at constant vestibular stimulus and constant speed of slow component cannot be brought about without a simultaneous change in amplitude. Such a variation can only be caused by changes of the time for interruptions of the slow phases by the centrally controlled fast phases. Early interruptions must then give an increase of the frequency and a decrease of the amplitude while late interruptions may give the opposite pattern. It is therefore of interest to find out if such variations

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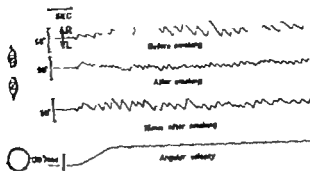


FIG. 1. (Horizontal eye movements) / clockwise rotation / darkness with pen eyes.

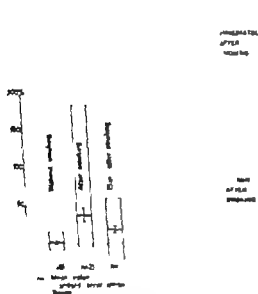


FIG. 2.

FIG. 2. Average difference of nystagmus frequency (beats per ten seconds) / per cent of difference between slow and fast after 1 rot from three minutes rest without smoking; B, let eyes be closed before and immediately after smoking; C, let eyes be closed before and fifteen minutes after smoking.

FIG. 3. Mean increment of nystagmus frequency (beats per ten seconds) after smoking as per cent of mean frequency without smoking, at ten different intervals of rotation and for three groups with different smoking habits. A, First occasion; B, second occasion; C, third occasion.

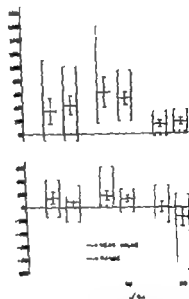


FIG. 3.

itude was seen. The speed of the slow component and the deviation of the eyes in the direction of the fast component were not affected, while the speed of the fast component showed a marked decrease. The rotations caused negligible angular deviation of the head before as well as after smoking. Fifteen minutes after smoking the nystagmus had not fully regained its pre-smoking pattern. The values at this time however did not differ significantly from those before smoking.

### *Recordings*

The movements and the position of the eyes were recorded by means of a DC-technique described by Lundgren Tibbling & Henriksson (1967). This technique allows registration of the horizontal nystagmus movements and the degree of deviation of the eyes. The movements and positions of the head were recorded by means of a potentiometer on the head of the test subject and the angular velocity of the rotation device by means of a technique based on a frequency rate principle. All recordings were made on a 4-channel ink writer (Vingograf 81 Elema Sweden).

### *Analysis of the Tracings*

The nystagmus tracings were analyzed at 2, 4, 10, 18 and 30 seconds after the onset of the acceleration with respect to frequency, amplitude, speed of fast and slow components, and position of the eyes. The frequency was determined by counting the number and the fractions of the nystagmus beats per second at the different times and also during the first ten seconds immediately after the start of the rotation. To get a representative expression of the amplitude this was calculated at each time as the average amplitude of three or more consecutive amplitudes. The speeds of the fast and slow components were calculated from the DC-tracings as degrees per second.

The deviation of the eyes was measured at the end of the fast component and calculated as the angular displacement from the mid position of the eyes. For these calculations the drift potential apparently caused by the tobacco smoking had to be considered. Thus when the position of the eyes was measured after rotation and a drift potential exceeding five degrees per minute was found the calculated value was corrected with the assumption of a continuous drift.

### *Methods for Statistical Analysis*

At each of the three occasions of rotation and for each quality at 2, 4, 10, 18 and 30 seconds after the start of rotation the mean values with their standard deviations and standard error of means were calculated. The comparisons between the qualities before and after smoking were statistically evaluated by use of the "student's" *t* test.

## RESULTS

The nystagmus pattern showed very pronounced changes after smoking as can be seen in Fig. 1. The analyzed qualities are summarized in Table 1. The frequency was the quality which showed the greatest change. This change was most significant during the fourth and tenth seconds after the start of the rotation that took place immediately after smoking. Together with the increase in frequency a corresponding decrease in ampli-

Table 1 (cont.)

Sec. after start of rotation	Amplitude	Frequency	Speed of slow comp.	Speed of fast comp.	Deviation
10	12.7 ± 3.0 (5.9-23.6)	2.5 ± 0.1 (1.5-3.2)	35 ± 18 (10-68)	216 ± 10 (148-360)	10.8 ± 2.5 (-8-33)
15	11.1 ± 0.9 (8.0-20.5)	2.1 ± 0.1 (1.0-3.1)	26 ± 3 (4-48)	100 ± 11 (70-206)	11.4 ± 2.3 (-8-32)
30	8.2 ± 0.9 (0.0-15.0)	1.3 ± 0.1 (0.0-2.5)	13 ± 2 (0-30)	101 ± 12 (70-260)	9.3 ± 2.4 (-10-29)

To get a more simple method of measuring the frequency this was determined during the first ten seconds after start of rotation. In Fig 2 the mean increment of the frequency immediately after and fifteen minutes after smoking is given in per cent of the mean frequency before smoking. Although there were great variations in the individual values, the mean increment from before to immediately after smoking was statistically highly significant ( $p > 0.001$ ) whereas there was no statistical difference between the values obtained before and fifteen minutes after smoking. On comparison very slight changes were found in the nystagmus pattern when ten subjects were rotated without smoking at three consecutive occasions with intervals of three minutes (Fig 3A). Repetition of the entire test showed good reproducibility (Table 2).

When the twenty-one test subjects were divided into three different groups according to their smoking habits, their nystagmus patterns after smoking were influenced in the same manner but to a varying extent (Table 2). Immediately after smoking, those who could be classified as occasional smokers showed a moderate increase in frequency of nystagmus (average 37%) while moderate smokers showed the largest (average 55%) and heavy smokers the least (average 16%) (Fig 3). Fifteen minutes after smoking, the frequencies in the occasional and moderate smokers had not returned to pre-smoking values, but the differences were not significant. On one occasion (Fig 3A) the mean frequency of the heavy smoker group was equal to the pre-smoking frequency while on another occasion (Fig 3B) it was even lower than the mean pre-smoking value. These differences, however, were not significant.

#### DISCUSSION

Verilux & Kruse (1961) have reported that spontaneous vertical nystagmus appears after smoking. In the present investigation of vestibular induced nystagmus we have recorded conspicuous changes in frequency and amplitude after smoking.

TABLE 1 *Effect of smoking on the per rotatory nystagmus pattern in 21 subjects*

Mean values of amplitude (degrees) frequency (beats/sec) speed of low and fast component (degrees/sec) and eye deviation (degrees) are given with standard error of the mean and ranges at 2, 4, 10, 18 and 30 seconds after start of angular acceleration (120°/sec/1.8 sec). *p*-values refer to comparison between values found before and immediately after or fifteen minutes after smoking.

Horizontal bars represent *p*-values > 0.05

Sec. after start of rotation	Amplitude	Frequency	Speed of slow comp.	Speed of fast comp.	Deviation
<i>Before smoking</i>					
2	13.3±0.9 (6.6-21.6)	3.0±0.2 (1.0-4.5)	52±3 (34-80)	195±10 (98-183)	13.1±1.3 (-4-30)
4	13.1±0.8 (5.2-20.0)	2.7±0.1 (1.7-3.6)	49±3 (32-80)	204±11 (75-285)	7.1±1.8 (-8-20)
10	12.7±1.0 (6.0-23.8)	2.4±0.1 (0.8-3.1)	39±3 (18-70)	202±12 (128-335)	3.0±1.3 (-8-14)
18	11.5±0.9 (4.6-19.5)	1.9±0.1 (0.9-2.9)	27±3 (8-60)	170±9 (75-250)	4.1±1.6 (-6-20)
30	8.5±1.0 (0.0-17.6)	1.3±0.1 (0.0-2.0)	16±2 (4-40)	155±10 (49-245)	1.6±2.7 (-20-28)
<i>Immediately after smoking</i>					
2	10.8±1.0 (2.0-24.5)	3.8±0.3 (1.9-7.6) <i>p</i> < 0.02	61±4 (28-92)	163±14 (38-320)	9.0±2.7 (-16-30)
4	10.4±0.9 (4.4-18.0) <i>p</i> < 0.05	3.7±0.3 (1.9-6.5) <i>p</i> < 0.005	48±4 (24-80)	167±12 (60-260) <i>p</i> < 0.05	5.7±2.3 (-24-22)
10	9.9±1.1 (4.6-28.4)	3.0±0.1 (2.0-4.0) <i>p</i> = 0.001	35±3 (17-64)	157±11 (73-255) <i>p</i> < 0.01	4.7±2.4 (-20-22)
18	8.0±0.8 (3.0-17.2) <i>p</i> < 0.01	2.3±0.1 (1.2-3.2) <i>p</i> < 0.02	22±3 (9-43)	139±10 (0-220)	3.4±2.6 (-16-36)
30	5.9±0.8 (0.0-16.0) <i>p</i> < 0.05	1.2±0.2 (0.0-2.4)	10±2 (0-26)	136±8 (80-185)	6.1±2.3 (-10-42)
<i>15 minutes after smoking</i>					
2	14.9±0.9 (7.2-23.5)	3.1±0.2 (2.2-4.0)	60±4 (24-82)	231±9 (16-336)	17.3±2.2 (3-40)
4	14.0±1.1 (5.6-25.5)	3.0±0.1 (2.0-4.5)	52±4 (19-86)	229±11 (148-360)	11.5±2.1 (-3-34)

Table 1 (cont.)

Sec. after start of rotation	Amplitude	Frequency	Speed of slow comp.	Speed of fast comp.	Deflection
10	12.7 ± 1.0 (9.9-23.4)	2.5 ± 0.1 (1.5-3.3)	25 ± 16 (10-68)	210 ± 10 (148-360)	10.8 ± 2.0 (-8-3)
III	11.1 ± 0.9 (8.0-20.5)	2.1 ± 0.1 (1.0-3.1)	26 ± 3 (4-48)	190 ± 11 (70-296)	11.1 ± 2.3 (-8-32)
30	8.2 ± 0.9 (0.0-13.0)	1.3 ± 0.1 (0.0-2.5)	13 ± 2 (0-30)	161 ± 12 (1-280)	0.3 ± 2.1 (-10-29)

To get a more simple method of measuring the frequency this was determined during the first ten seconds after start of rotation. In Fig. 2 the mean increment of the frequency immediately after and fifteen minutes after smoking is given in per cent of the mean frequency before smoking. Although there were great variations in the individual values, the mean increment from before to immediately after smoking was statistically highly significant ( $p > 0.001$ ) whereas there was no statistical difference between the values obtained before and fifteen minutes after smoking. On comparison very slight changes were found in the nystagmus pattern when ten subjects were rotated without smoking at three consecutive occasions with intervals of three minutes (Fig. 3 A). Repetition of the entire test showed good reproducibility (Table 2).

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Horizontal bars represent *p*-values > 0.05

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2	10.8±1.0 (2.0-24.5)	3.8±0.3 (1.9-7.6)	61±4 (28-92)	103±14 (38-320)	9.0±2.7 (-18-30)
	—	<i>p</i> < 0.02	—	—	—
4	10.4±0.9 (4.4-18.0)	3.7±0.3 (1.9-6.5)	48±4 (24-80)	167±12 (63-260)	5.7±2.3 (-21-22)
	<i>p</i> < 0.05	<i>p</i> < 0.005	—	<i>p</i> < 0.05	—
10	9.9±1.1 (1.6-26.4)	3.0±0.1 (2.0-4.0)	33±3 (17-64)	157±11 (75-235)	4.7±2.4 (-20-22)
	—	<i>p</i> < 0.001	—	<i>p</i> < 0.01	—
18	8.0±0.8 (3.0-17.2)	2.3±0.1 (1.2-3.2)	22±3 (9-43)	139±10 (0-220)	3.4±2.6 (-16-36)
	<i>p</i> < 0.01	<i>p</i> < 0.02	—	—	—
30	5.9±0.8 (0.0-16.0)	1.2±0.2 (0.0-4)	10±2 (0-26)	136±8 (56-185)	6.1±2.3 (-10-42)
	<i>p</i> < 0.03	—	—	—	—
<i>15 minutes after smoking</i>					
2	14.9±0.9 (7.2-23.5)	3.1±0.2 (2.2-5.0)	60±4 (24-82)	231±9 (16-336)	1.3±2.3 (3-10)
	—	—	—	—	—
4	14.0±1.1 (5.8-25.5)	3.0±0.1 (2.1-4.5)	52±4 (19-86)	229±11 (148-360)	11±2.1 (-3-34)
	—	—	—	—	—

not only with respect to its velocity but also in respect to its ability to interrupt the slow phase. Thus the frequency and the amplitude must depend not only on variations in the vestibular stimulus, but also on the activity of the parts of the brain stem which are engaged in initiating the fast phases.

It is possible that the changes obtained in the frequency-amplitude pattern may be due to a decrease in wakefulness causing a deviation of the eyes in the direction of the slow component. Such a deviation could be expected to diminish the amplitude at least at extreme deviation. However, as smoking has been found to change the EEG-pattern (Yamamoto & Domino, 1964) in a way indicating an increase of alertness, a deviation in the direction of the slow component cannot be expected. Further, our technique allows us to measure the position of the eyes during the whole test and no such deviation was found. Therefore an explanation for the changes in the nystagmus pattern must be looked for in other mechanisms. A decrease of the velocity of the fast phase would tend to lower the frequency instead of increasing it. In spite of this, our results show an enhancement of the frequency after smoking. Therefore, variation in the time interval for the interruption of the slow component by the fast phase must be the main source for the changes in the nystagmus pattern.

From our results we conclude that it is possible to influence selectively the centrally induced fast phase without affecting the slow one. Thus, while the speed of slow component and the deviation in the direction of the fast phase are expressions of the peripheral sensitivity the frequency pattern can be used as a tool for studying the conditions within the central nervous system.

The pharmacological background for the changes found in the nystagmus pattern is at the present time difficult to explain. Probably the inhaled nicotine may in some way cause variations in the blood supply to certain brain areas which, as a consequence, will influence the nystagmus. The changes of the nystagmus pattern can also be attributed to a direct effect of nicotine on the nervous cells or on central synapses. However, a combination of the mechanisms mentioned cannot be excluded. A further possibility might be that the concentration of carboxy-hemoglobin in the blood after smoking tends to decrease the oxygen supply to the brain tissue. Carbon monoxide, however, is eliminated rather slowly (about 15-20 % per hour by normal ventilation) while the changes of the nystagmus pattern described had reverted to normal in about half an hour.

The occasional smokers, as compared to the moderate smokers, showed only a moderate increase in frequency per ten seconds after smoking. This may be related to the fact that occasional smokers do not inhale the smoke from the cigarette deeply enough and therefore absorb less nicotine through the lungs (Larson 1960).

The fact that there was only a moderate increase in frequency in the heavy smokers may be explained by a central habituation effect of smoke.

TABLE 2 *Effect of smoking on the per rotatory nystagmus patterns obtained from three groups of subjects with different smoking habits*

Mean value of frequency with standard error of mean and ranges are given before, immediately and fifteen minutes after smoking. *p*-values refer to comparison between values found before and immediately after, fifteen minutes after and 15 min after. Horizontal bars represent *p*-values > 0.05.

Cig./day	Occasion	Frequency (beats/10 sec.)		
		Before smoking	Immediately after smoking	15 min after smoking
0-4	I	25.3 ± 1.8 (19-34)	32.9 ± 3.0 (22-46)	28.1 ± 1.4 (24-35)
	II	27.3 ± 1.5 (23-33)	39.3 ± 4.7 (21-60) <i>p</i> < 0.05	29.4 ± 2.7 (18-40) —
5-10	I	25.3 ± 1.5 (20-33)	39.9 ± 3.5 (29-57) <i>p</i> < 0.05	29.4 ± 1.0 (20-33) —
	II	28.1 ± 1.2 (24-32)	43.1 ± 3.6 (32-62) <i>p</i> < 0.05	31.4 ± 1.0 (27-40) —
11-20	I	28.3 ± 1.3 (24-34)	32.3 ± 1.8 (24-39) —	28.6 ± 2.5 (21-38) —
	II	30.0 ± 1.9 (23-39)	35.4 ± 2.3 (24-43) —	28.6 ± 2.9 (22-41) —

The analysis of the influence of smoking on the vestibular nystagmus pattern shows that the two qualities reflecting the peripheral stimulus, the speed of the slow component and the deviation in the direction of the fast component, are quite unaffected. On the other hand, the speed of the fast component, which has been proven to be generated by the CNS (McCabe 1965), decreases markedly. Such a decrease was also found by de Kleyn & Versteegh (1922) in induced caloric nystagmus in rabbits, when toxic doses of nicotine were administered. In the present study, in spite of a constant vestibular stimulus in different tests, and in spite of identical vestibular responses, judged from the speed of the slow component, the frequency increased and the amplitude decreased immediately after smoking. This can only be brought about by the fast phase interrupting the slow one more frequently. This indicates that the fast phase is changed by smoking.



## TELEMETRY SYSTEM FOR NYSTAGMUS RECORDING

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ENG is the most satisfactory method for nystagmus recording and for scientific purposes it has been developed to the point where it is a very reliable tool. Simplified commercial types of ENG apparatus are available and permit recordings of vestibular examination so that all relevant parameters can be registered objectively. The advent of special types of semiconductors has permitted the construction of telemetry systems for ENG. One of the advantages of using radio transmission is, *inter alia*, that otolith-ocular as well as vestibulo-spinal reactions may be investigated simultaneously.

Högyes (1881) in his studies on the connection of the labyrinth with the ocular muscle nuclei, was the first to describe a method by which ocular movements could be recorded via a pneumatic system on a revolving smoked drum. Berlin (1891) was the first to record nystagmus in man. The principle of his method was to place on the cornea an ivory shell connected with a brush hair which recorded the ocular movements on a watch glass. Buys (1900) and Ohm (1914) also used mechanical principles, but utilized the movement transmitted to the upper eyelid due to the difference in the curvature of the cornea and sclera on movements of the eyeball.

A number of photographic methods were described, *inter alia* by Dohlman (1925) one of the few to obtain good results thereby. Kristensen & Elstorf-Pedersen (1933) used an ophthalmograph for cinematographic registration of the eye movements. However these methods were not clinically applicable. In 1931 Torok *et al* introduced the photoelectric method (PENg) based upon the difference in the reflection of light from the cornea and sclera. This method has not, however come into major use in daily clinical work.

Electro-oculography (ENG) was first described by Scholtz in 1922. ENG is based on the cornea-retinal potential difference and has become a clinically applicable method. Great progress has been made by ENG, *inter alia* in the research of Aachen *et al* (1956) Henriksen (1958) and Mouton & Rusbach (1956). To-day it is an indispensable clinical aid, especially in examining patients with weak vestibular disturbances.

In recent years transistorization of the ENG apparatus has led to the development of miniature, high quality amplifiers and new types of re-

ing. As a consequence this may indicate that heavy smokers obtain less stimulation by their smoking than do the moderate smokers.

For a proper understanding of the variations in the nystagmus pattern obtained after smoking in subjects with different smoking habits, a more extended investigation is in progress.

### ZUSAMMENFASSUNG

Das vestibuläre Nystagmusemuster zeigte deutliche Veränderungen nach Zigarettenrauchen. Diese Veränderungen könnten den zentralen Einflüssen zugeschrieben werden. Es hat sich gezeigt, dass die schnelle Phase die langsame Phase beeinflusst hat dadurch dass die Schnelligkeit der schnellen Phase und insbesondere der Abbruch der langsamen Phase von der schnellen verändert wurden. Frühzeitiger Abbruch ergaben eine erhöhte Frequenz und eine gesenkte Amplitude. Die im vestibulären Rezeptor initiierten Qualitäten — die Schnelligkeit der langsamen Komponente und die Augendeformationen in der Richtung der schnellen Phase — waren nicht signifikant verändert. Die obengenannten Qualitäten wurden verwertet, um den Mechanismus der zentralen induzierten schnellen Phase zu erklären. Starke Raucher demonstrierten im Muster des vestibulären Nystagmus weniger Veränderungen beim Rauchen als mässige Raucher.

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Fig. 2. Person connected with FM transmitter

type E35P002. In order to ascertain the tuning accuracy an indicator instrument was connected to the Foster Seeley discriminator of the IF amplifier. The frequency stability was controlled by means of an AFC (automatic frequency control) circuit. The detected ENG signal was recovered directly from the output terminals of the discriminator.

#### Recording Equipment

The signals were recorded both on a mingograph 24 and a Tektronix 502 Oscilloscope. With the mingograph in position D (DC-amplifier) the telemetry system used has a time constant of 2 sec. In position A (AC-amplifier) of 1 sec.

#### RESULTS

Fig. 4 gives some transmitted curves. The transmitting distance was 25 m. Curve A shows the appearance of a number of calibration pulses. Curves B and C show caloric and postrotatory nystagmus respectively. The time constant is 1 sec. Curve D is from a patient with a post-concussion syndrome showing spontaneous nystagmus present only in the dark or behind closed eyelids. The time constant was 2 sec.

#### COMMENTS

It has been the purpose of the present study to demonstrate the possibility of using telemetry systems for transmitting ENG signals. The

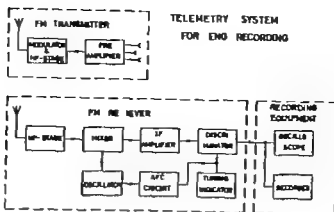


FIG. 1 Diagram showing telemetry equipment

recording techniques. One possibility is the transmission of the signals via radiotelemetry. The purpose of the present paper has been to evaluate such a method in practical use.

### Apparatus and Method

The potentials to be recorded in the ENG are usually in the range 50–100 microvolts and thus put great demands upon the internal noise of the amplification system, the time constant of the amplifier and the common mode rejection of the circuit. These demands can be met by using transistors with particularly low noise and the employment of differential coupled amplifiers.

Furthermore it is important that the frequency range of the transmitter is wide enough to transfer the signal without undue distortion and that the output of the transmitter is suitable with the natural limitation, that it must not disturb other systems. Fig. 1 gives a block diagram of the telemetry equipment developed in our department.

#### Transmitter

The ENG potentials from the patient are amplified in a differential amplifier with the following specifications (Fryer & Deboo, 1965): Input impedance 10 megaohms, gain 00 dB, common mode rejection 80 dB. The amplified ENG signals are used to modulate the HF stage of the FM transmitter. The modulation signals cause small changes in the emitter current and the collector-emitter voltage. This changes the collector-emitter capacity and thus gives the desired frequency swing (Roy & Hart 1960). The oscillator frequency may be adjusted between 88–100 MHz by means of a variable capacitor in the tank circuit of the HF stage. The FM transmitter has a maximum range of 100 m.

#### FM Receiver

The receiver (Fig. 3) was constructed from commercial components and consisted of a Torotor FM Tuner type FE 31AA and Torotor IF amplifier

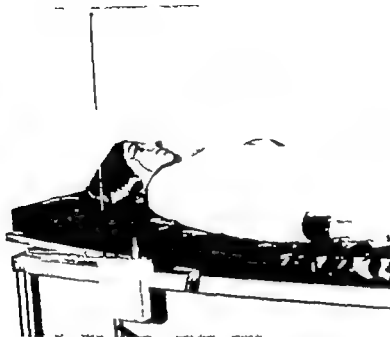


FIG. 2. Person connected with FM transmitter

type E55P002. In order to ascertain the tuning accuracy an indicator instrument was connected to the Foster Seeley discriminator of the IF amplifier. The frequency stability was controlled by means of an AFC (automatic frequency control) circuit. The detected ENG signal was recovered directly from the output terminals of the discriminator.

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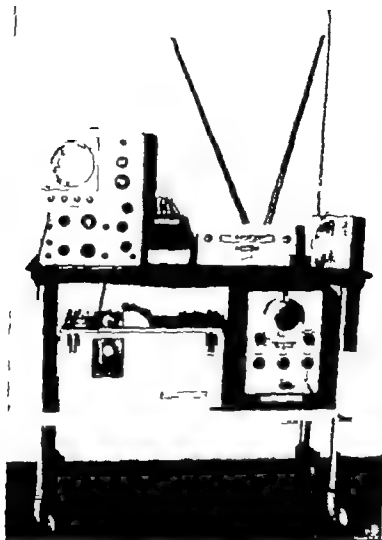


FIG. 3 FM receiver with recording equipment

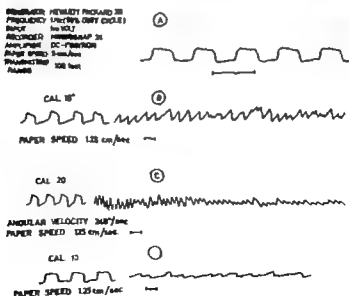


FIG. 4 Nystagmus curves traced by means of a film meter. A Calibration curve. B. Normal nystagmus. C. Postrotatory nystagmus. D. Postneurotic nystagmus.



quality of the curves is of such a standard that the different parameters such as maximum eyespeed, frequency and duration, can be calculated in an entirely adequate way.

There are several advantages in using telemetry in ENG. The study itself and the tracing of the curves need not take place in the same room. This may be practical in examining debilitated or dizzy patients, as they can remain in their beds. Telemetry can be done directly from patients on the operating table during operations on, e.g., the stapes or during ultrasonic treatment of the vestibular organ.

The portable FM transmitter permits the simultaneous investigation of several vestibular reactions, such as nystagmus on the one hand and pointing deviation, blindfold walking, Romberg's test or the stepping test (Peitersen, 1962) on the other.

Finally telemetry may facilitate recordings when using rotation chairs for vestibular tests, as it obviates the disadvantages of the springing contacts. It is too early to say whether telemetry is going to gain ground within ENG in the same way as within ECG, but from a technical point of view there is nothing to prevent this.

### ZUSAMMENFASSUNG

Die Elektro nystagmographie (ENG) ist bis jetzt die beste und verbreitetste aller Methoden zur Nystagmusregistrierung — und die die zu den besten Ergebnissen geführt hat. Die kommerziell hergestellte ENG-Apparatur ist vereinfacht worden, so dass sie für Vestibularisuntersuchungen verwendet werden kann sowie die Parameter mit genügender Qualität wiedergibt, woran man interessiert ist. Die Herstellung spezieller Transistortypen hat die Konstruktion von telemetrischen Systemen für ENG ermöglicht. Der Vorteil der Technik gegenüber der konventionellen Nystagmusregistrierung ist u.a., dass sowohl die vestibulo-oculären als die vestibulo-spinalen Reaktionen gleichzeitig untersucht werden können.

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## Acta Oto Laryngologica 50 years

It is common knowledge that the creation of *Acta Oto-Laryngologica* is to be ascribed entirely to Gunnar Holmgren. Chiefly with a view to strengthening co-operation between oto-rhino-laryngologists in Scandinavia Holmgren started *Oto-Laryngologiska Meddelanden* in 1912 and *Nordisk Tidskrift för Oto-Rhino-Laryngologi* in 1916. It soon became evident that these journals were of great importance for furthering scientific research in Scandinavia. Difficulties did, however, arise in getting the original articles reviewed in the international literature. Holmgren therefore decided, in 1918, to present a new journal, *Acta Oto-Laryngologica* with papers written in English, French, and German. Subsequently in collaboration with colleagues in numerous countries, *Acta Oto-Laryngologica* developed into a leading specialist journal. Holmgren emphasized at an early stage that an essential feature was, precisely collaboration with many countries abroad—a fact that has been amply confirmed during the whole life of the journal.



Gunnar Holmgren



Paul Frenckner

In addition to the regular issues of *Acta Oto Laryngologica* the numerous supplements have proved to give our readers fundamental surveys and monographs in current fields of research. Hitherto 250 supplements have been published. Many of them are theses for the doctorate of medicine from the Scandinavian countries and have made outstanding contributions to questions of topical interest.

It is the hope of the Editorial Board of *Acta Oto-Laryngologica* that we will in the future be able to continue in the same spirit, and with the same success, as our founder Gunnar Holmgren and his successor Paul Frenckner

C. A. Hamberger  
Editor in Chief

## AUDIOMETRIC IDENTIFICATION OF NORMAL HEARING CARRIERS OF GENES FOR DEAFNESS

H. ANDERSON and E. WEDENBERG

*From the Departments of Otolaryngology and Audiology Karolinska Spkhuset  
Stockholm, Sweden*

As most carriers of genes for recessive deafness do not display hearing impairment to a greater extent than a average it is impossible to identify suspected gene carriers by ordinary audiometry. In the study reported here more advanced test methods, namely Békésy audiometry and the stapedius reflex test, have been applied in an attempt to detect any subclinical peculiarities in the hearing. The material consisted of a group of 30 parental pairs with normal hearing and a strong indication of genetic deafness; they had 74 children. 47 of them with severe genetic hearing impairment or total deafness. On comparison with a control group two peculiarities were found in the hereditary series, namely small but distinct dip in the middle frequency range of the hearing threshold and abnormally high thresholds for the acoustically elicited stapedius reflex.

The observations are discussed against the background of earlier genetic and histologic findings.

Deafness in children is not a unitary clinical concept: rather the term covers a group of distinct pathologic conditions whose causes are to be sought among a number of factors and agents and where the auditory system may have been damaged at widely separated sites and at quite different ages—even *in utero*.

Deafness is divided into two main groups according to whether it is hereditary or acquired. Pre-, per- and postnatal sub-groups are recognized, according to the time of onset. Congenital hearing defects may be either hereditary or acquired and either pre- or perinatal.

It has hitherto been extremely difficult to identify the cause of childhood deafness in the individual case. The classification is made on the basis of the medico-audiologic examination and the history, and especially the family history (Look at the family rather than at the individual said Alexander Graham Bell in 1891). The forthcoming information relating to deaf relatives must be weighed against any potentially detrimental exogenous factors that might be considered to have a bearing on the child's hearing before, during or after birth, and against the objective findings of the examination. In some cases a hereditary background is so obvious that the hearing defect may be ascribed an endogenous cause. Often, how-

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Editor in Chief

Hereditary deafness satisfies the four postulated conditions for inborn errors of metabolism

Provided that the tests are subtle enough, many hereditary diseases may be disclosed in their symptomfree carriers by minor deviations from the normal. If a person is a heterozygote for a complaint he has one normal and one mutant gene. Since each gene is responsible for the formation of its own protein which is often an enzyme, in the case of a changed genetic structure the mutant gene will either have prevented the formation of this particular enzyme or it will have given rise to an abnormal enzyme.

There are, however, no biochemical tests by which it is possible to detect any abnormal activity in enzymes responsible for the development and function of the auditory system. For this reason it has not been possible to class hereditary deafness as an inborn error of metabolism but this does not rule out the possibility that it belongs to this group. It means only that our knowledge of the involvement of these enzymes in the biologic process is still too limited to be able to ascertain the biochemical basis of these defects.

There remains the possibility of demonstrating the effect of any enzymatic defects on the hearing organ in gene carriers by audiometric studies. Such attempts have been made in order to detect heterozygotes among the parents of children considered to have a genetic hearing impairment (Wildervanck, 1937; Fraser 1964). From an examination of 15 normal hearing parental pairs with their 32 children with recessive deafness Wildervanck inferred that it was impossible by ordinary audiometry to identify these parents as heterozygotes. "The conclusion of my entire investigation is that normal hearing parents of children with deafness are not detectable as heterozygotes." Nor could Fraser find any significant hearing impairment in heterozygotes in sex linked recessive deafness. It may thus be assumed that any hearing defects in the heterozygotes are subclinical and that to obtain a solution of the problem more refined methods than have been used so far must be applied.

The present study constitutes an attempt by advanced audiometric techniques to identify carriers of mutant recessive and intermediate genes of deafness and thus to obtain a better impression of the mode of inheritance of this condition than has hitherto been possible.

## METHODS

In earlier attempts to identify heterozygotes of deafness by audiometric method, reliance has been placed solely on octave audiometry. This method is sensitive enough to disclose clinical defects, but this was not the case in the supposed heterozygotes in whom any defects would have been subclinical. However, no previous study has been made of how these respond to more advanced or sensitive tests. Such a subtle test is provided by the Békésy audiometry where, by the continuous recording of the hearing

ever no cause of the hearing impairment can be found and the case must then be assigned to the "unknown group" but there is every reason to suppose that in this group too the hearing defect will usually have a genetic origin.

In short, the consensus is that the hereditary group comprises about one half of all the child cases of severe hearing impairment. In the hereditary group the recessive subgroup is by far the largest. Opinions diverge, however, on the frequency of recessive hearing impairments in hereditary deafness. Arnvig (1953) gives more than 90 per cent, with about 5 per cent dominant while Fraser (1964) puts the figure at more than 70 per cent with 25 per cent dominant and a small number of sex linked.

On the mode of inheritance of deafness numerous theories have been proposed (Lundborg 1912, 1920; Albrecht 1922; Dahlberg, 1931; Hammerschlag, 1932, 1934; Johnsen, 1952). The dominant form has been the subject of many studies over years (Stephens & Dolowitz, 1949; van Egmond, 1954; Mårtensson, 1960; Wildervanck 1962; Huizing *et al.* 1966) and here the detection of carriers presents no problem, just as is the case for other dominant genetic defects.

These theories have not so far, however, yielded any explanation of the mode of inheritance in the commonest type of hearing defect, the recessive sensory neural hearing impairment. Many families have been described in which both parents were recessively deaf but whose children all had normal hearing (Hammerschlag, 1934; Lehmann 1950). It must therefore be assumed that there are several if not many different genes situated in different loci and that in the homozygotic form they give rise to deafness. It is thus justified to speak of the recessive forms of deafness. Opinions differ on the number of loci for such abnormal genes which can give rise to recessive deafness. Chung *et al.* (1959) who carried out an analysis of a series collected by Stevenson & Cheeseman (1906) assessed their number at 36 while Sank (1963) put it considerably higher "at least 40".

Of the causal connection between defective genes and hereditary deafness we know still less than about the mode of inheritance. In our search for an approach to the investigation of these causes interest has been focused on a type of disease where an enzyme defect is the underlying cause, namely inborn errors of metabolism.

This term was coined as early as 1908 by Sir Archibald Garrod, the English physician, for a pathologic entity comprising the 4 diseases albinism, alkaptonuria, cystinuria and pentosuria. They had certain common traits: (1) They could be demonstrated in the first days of life. (2) they tended to occur frequently in certain families in a large number of cases. (3) they were fairly benign and compatible with a normal length of life. (4) they often appeared in the offspring of consanguineous marriages. Garrod's prophecy that the underlying cause of these diseases would prove to be an enzyme defect has proved correct. From the original number of 4 the inborn errors have now increased to more than a hundred (Hsia 1966).



be misled by or confused with, exogenous defects. For instance those parental pairs were excluded a member of which showed anamnestic and audiometrically characteristic impairment of obviously exogenous causation (conductive impairment defects through middle ear drugs, etc.) to an extent that interfered with the evaluation of the result. The only kind of threshold elevation of possible exogenous origin to be accepted was the hearing impairment at higher frequencies associated with age—presbycusis—which is well known and extensively documented. This exception was necessary because the parent group was heterogeneous with respect to age. The parents' hearing threshold was therefore in this respect assessed in relation to the mean for the corresponding age and sex groups of the Wisconsin State Fair Hearing Survey (WSFHS, Glorig *et al.* 1937) after appropriate correction for difference in calibration of audiometers. For the difference in audiometric methods (Békésy and octave audiometry) however no correction was made.

(3) Both marriage partners should be available and willing to undergo examination.

For practical reasons the study was limited to parents consulting the Department of Audiology, Karolinska Hospital for their children's deafness. To obtain some measure of randomness in the selection such parental pairs resident in a certain geographical area were supplemented with an equal number of pairs chosen in order of registration at the Department, irrespective of their place of residence.

After the selection on the basis of the above criteria there remained in the geographic group 15 families resident in the area served by the Manila School for the Deaf. These constituted all the recorded subjects in the area who satisfied the above criteria. The 15 families had 44 children (28 boys, 16 girls); 25 of whom were deaf (18 boys, 7 girls). The other data are presented in Table 4.

The chronologic group consisted of 15 families from the clientele who consulted the Department during 1964–65 and who likewise satisfied the above criteria. These families had 30 children (14 girls, 16 boys); 22 of whom were deaf (13 boys, 9 girls). Other details are given in Table 4.

The hereditary series of parents thus consisted altogether of 30 families with 74 children, 47 of whom were deaf (totally or profoundly hard of hearing). The age of the parents at the time of the study ranged from 21 to 71 years for the men (mean 42.8) and 22 to 65 years for the women (mean 35.9).

The presence of a genetic background is confirmed by the fact that in less than 14 of the families had 2 or more children with impaired hearing. In 12 of the families there was, moreover, information on hearing defects in other relatives, though not with a dominant mode of inheritance.

Of the 47 children 32 were totally deaf and 15 had severe hearing impairment, but with measurable residual hearing. In 10 of these 15 the hearing impairment had progressed during an observation period of more than 10 years. Such progress has been found to be a distinctive feature of

threshold it is possible to observe even small peculiarities or deviations. Another possibility is to subject the auditory system to a certain load by a test well above the threshold with the object of detecting defects that are not manifested in the threshold test. This possibility is provided by determination of the threshold for the stapedius reflex, a method that also has the advantage of objectivity.

All subjects in the present study were submitted to a carefully ear examination and relevant medical history were recorded. The hearing tests were performed in a sound proof chamber by an experienced operator. The hearing thresholds (125–8000 Hz) were recorded with the Grason-Stadler Békésy audiometer type E 800 calibrated in accordance with the ISO standard (R 389 1964).

The stapedius reflex was recorded by the technique described by Klockhoff & Anderson (1959) and Klockhoff (1961). The acoustic stimulus was delivered by an octave tone audiometer calibrated in accordance with ISO standard R 389 and satisfying the requirement of ICE Recommendation no 177 (1965). The threshold for the stapedius reflex was established for the test tone octaves 125–4000 Hz and half octaves 1500 and 3000 Hz. The determinations were made in 5-dB steps and the maximum available output for 500–4000 Hz was 120 dB and for 250 Hz, 100 dB (hearing level). The reflex measurements enable the presence also of minor conductive impairments to be excluded with a high level of reliability (Klockhoff & Anderson 1959, Klockhoff 1961) an important fact for the evaluation of the test results.

## MATERIAL

### *Hereditary series*

The hereditary series consisted of parental pairs with at least one child with deafness that was judged to be endogenous. Since the object of the study was to detect recessive and intermediate carriers, all families with a dominant mode of inheritance were excluded. Unlike the dominant carrier the recessive and intermediate ones are known to be free from symptoms and for this reason only those presumed gene carriers with subjectively normal hearing were included in the series.

The following criteria were applied in selecting the parental pairs.

(1) The children's deafness should be classified as "probably endogenous". This means that the case history and the examination disclosed no exogenous cause of the defect and that (i) the child had siblings with defective hearing of likewise unknown cause, and/or (ii) that the examination revealed an apparently high incidence of "inexplicable" hearing impairments of an early onset in the parents' relations.

(2) The parents' hearing should be subjectively normal.

As has been pointed out earlier the recessive and intermediate heterozygotes are assumed to display no clinical signs or symptoms. For any subclinical endogenous peculiarities to be detectable by means of hearing tests they should not

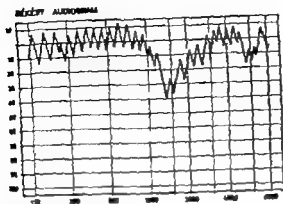


Fig. 1. Example of dip in hearing threshold recorded by Békésy-audiometry. Note that its position is such that the significant characteristic of the dip might be missed in routine octave audiometry (family No. 28, mother left ear).

parents also proved to have audiometrically normal hearing or in some cases, extremely slight defects. To assess the possibility of there being an exogenous or endogenous cause of these small irregularities in the hearing threshold curves the authors considered it appropriate in the analysis to divide them into two frequency ranges

(1) 3000–6000 Hz which has been found to be the most vulnerable to exogenous agents and where presbycusis sets in

(2) 250–3000 Hz which is extremely resistant to exogenous agents and where impairments caused by them are almost invariably noticed only when the hearing in the upper frequency range is severely impaired. This destruction pattern is also characteristic of presbycusis: the high frequency range is invariably severely impaired before the lower range is affected.

In order to find whether the hearing threshold in the range 3000–6000 Hz might be regarded as average a comparison was made with the corresponding age and sex groups from the Wisconsin State Fair Hearing Survey (Glorig *et al.* 1957). It was found that for 56 of the 60 parents (93 per cent) the hearing lay within the semi-interquartile range; for 42 it was distinctly better than the median. For only 4 of the fathers did the threshold fall outside the 7 percentile at at least 2 frequencies, still without being high enough to make the subject aware of the impairment.

In the frequency range 250–3000 Hz, too, the parent series as a whole showed no significant elevation of the hearing threshold. However some of the subjects recorded well defined elevations in the otherwise normal hearing threshold although small, these "dips" were quite distinct and easily distinguishable in the Békésy recording. They varied in depth and extent to be classed as significant. It was stipulated that they should be at least 20 dB (hearing level) extend over at least one octave and be not

endogenous hearing defects (Barr & Wedenberg 1965) The markedly recessive nature of the series is confirmed by the severe hearing impairment of the probands in relation to the subjectively normal hearing of the parents, and the fact that no less than 3 of the marriages were between cousins.

### *Control groups*

To be able to decide whether a certain peculiarity in otherwise normal hearing might be considered as an endogenous stigma it is necessary to know its degree and incidence in an average population In this respect large scale studies on normal subjects are of little help since small individual variations are bound to disappear with the form of presentation generally used The presence of peculiarities in the hearing threshold was therefore examined by Békésy audiometry in a control series The selection followed the same general lines as for the hereditary series—that is to say—there should be subjective normal hearing while obviously exogenous perceptive and conductive impairment that might interfere with the observations were excluded Békésy audiometric examinations were carried out on 60 women and 73 men aged 21–24 years

This material was supplemented with an analysis of the results of an octave-audiometric screening study of 10 778 14 year-old school children (5623 boys, 5155 girls) from Stockholm schools Its purpose was to examine the hearing of a group before it was significantly exposed to exogenous strain Although the audiometric procedure used here was considerably less sensitive than the Békésy technique for detecting minor peculiarities in the hearing threshold—and hence less significant as test—this analysis was nonetheless regarded valuable as it shows the incidence of the features of interest in a young still "intact" group as determined with the most common form of audiometry

The subjects used in the study of individual deviations in the reflex threshold must fulfil extremely high requirements with respect to the hearing threshold This sharpening of the requirements was regarded necessary to exclude even slight signs of exogenous influence which are known first to appear as minor deviations in the threshold of hearing usually in the upper frequency range To be acceptable for the reflex test the subject was required to have not only perfect middle-ear condition but also a Békésy hearing threshold better than 15 dB in the range 250–4000 Hz, and better than 20 dB in the ranges 125–250 and 4000–8000 Hz Fifty of the women and 50 of the men meeting these requirements provided the control group for the stapedius reflex test

## RESULTS

### *Hearing threshold in the hereditary series*

A prerequisite for the hereditary loaded parental pairs to be accepted in this study was subjectively normal hearing The analysis shows that the

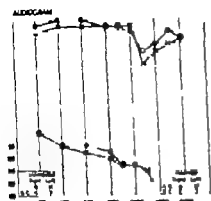


Fig. 2.

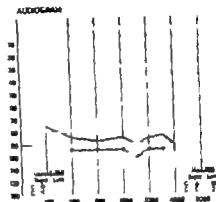


Fig. 3.

FIG. 2. Example of abnormally high reflex thresholds (dash-dotted). Values within shaded area are regarded as pathological (1 only No. 6, mother).

FIG. 3. Median and semi-interquartile range (shaded) of reflex thresholds in the 300 ears of the control group. Dashed curve indicates limit on and above which threshold value is regarded as pathologically high.

In the genetic series only a few cases were found to fall within this normal range. The stapedius threshold was considerably increased and at many points it could not be reached, even though the hearing thresholds of the subjects almost invariably lay within the normal range (Fig. 2).

It was checked that the cause of the elevation of the reflex threshold was located in the sensory system in the stimulus ear and not due to defects in the motor branch of the reflex arch or the middle ear system of the recording ear.

Such abnormally elevated reflex thresholds—determined on the basis of criteria specified below—were found in 16 fathers and 21 mothers in the parent group. Further details of the distribution of this property are given in Table 2.

#### *Reflex threshold in the control group*

*Criticism of pathologic limit.* That the majority of the reflex thresholds in the hereditary group were elevated was evident from a preliminary inspection.

TABLE 2. Distribution of subjects with pathologically high reflex thresholds

	Hereditary group		Control group	
	Male (n = 30)	Female (n = 30)	Male (n = 50)	Female (n = 50)
Younger group	6	11	2	1
Older group	10	10	—	—
Total	37 (62%)		3 (3%)	

less than 6 dB at the limits of this frequency range (Fig. 1). Such dips were recorded in 3 of the fathers (10 per cent) and 7 of the mothers (23 per cent). The dip centre was usually located at 1500–2000 Hz, with a depth of 20–30 dB and a range of about 1½ octaves. There seems to be no correlation between the presence of such dips and the age of the subject; they were however found in an appreciably greater percentage of the mothers than the fathers (Table 1).

#### *Hearing threshold in the control groups*

The presence of such sub-clinical threshold dips was examined in a control series consisting of 60 women and 73 men ranging in age from 21–34 years. The fact that they were found in only one woman and one man (< 2 per cent) indicates that they are normally very rare.

While continuous Békésy audiometry is the ideal method for detecting these dips it was considered of interest to examine whether these quite small changes in threshold are recordable by octave audiometry. These dips were found in less than 1 per cent of the audiograms for 10 778 14-year-old children (5623 boys, 5155 girls); there was no appreciable sex difference. As, however, this study was based on the results of octave audiometric screening only dips coinciding with the test frequencies and exceeding 20 dB could be detected. Where the anomaly was recorded as present it was confirmed by accurate audiometry.

#### *Reflex threshold in the hereditary series*

By means of Békésy audiometry it was thus possible in many cases to find in the threshold pattern a peculiarity that would appear to be of an endogenous nature and possibly indicative of endogenous deafness in the carrier. In other cases, however, no deviant feature was found in the hearing threshold. In the subsequent experiments, therefore, the auditory system was subjected to tests above the threshold in the hope that further distinctive characteristics might come to light. The test chosen was the stapedius reflex test in which contractions of the stapedius muscle are taken as a measure of the afferent inflow in the acoustic nerve, thus providing information on the capacity of the hearing organ at high levels.

It is known from previous studies that the reflex threshold in the frequency range 250–4000 Hz normally lies between 80 and 90 dB hearing level for the various test frequencies.

TABLE 1 *Distribution of subjects with hearing-threshold dips*

	Hereditary group		Control group	
	Male (n = 30)	Female (n = 30)	Male (n = 73)	Female (n = 60)
Younger group	2	3	1	1
Older group	1	3	—	—
Total	10 (17%)		2 (1.5%)	

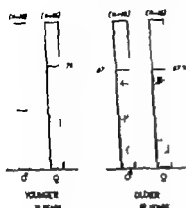


Fig. 4

Fig. 4 Distribution of cases with pathologically high reflex thresholds in the two age groups of the hereditary material.

Fig. 5. Observed and theoretical occurrence of pathologically high reflex thresholds in one or both marriage partners.

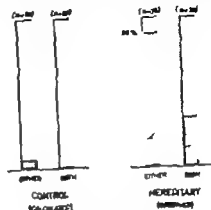


Fig. 5.

and in 4 subjects of the hereditary series. No appreciable difference in the figures for the two hereditary age groups is noted, however the number of dips was considerably greater for the mothers. As regards the distribution of the dips they were found in one or both partners in 9 marriages (27 per cent) and in both partners in one marriage.

The fairly common occurrence of dips in the parent series with a background of hereditary deafness, their rarity in the control series, the absence of any evident explanation for them in the medical history and their audiometric configuration all point to a genetic origin.

The occurrence of subjects with pathologically high reflex thresholds are given in Table 2. The distribution with respect to both age and sex was so similar in the two age groups that no clear trend was to be found (Fig. 4). In the parent group the peculiarity was bilateral in 3/4 of the cases. In the control group the 3 observed cases were all bilateral. In the marriages elevated reflex thresholds were found in at least one partner in 27 of them (90 per cent) and in both partners in 10 (33 per cent). There was no clear difference in this respect between the two age groups.

The parent group thus contained a much greater percentage of elevated reflex thresholds than would be expected in a normal parent population as represented by the control group (Fig. 5). The elevation cannot be ascribed to any known exogenous factor.

More than 7 of the 10 subjects in the parent group where the threshold dip was found also recorded abnormally high reflex thresholds. This would indicate that the underlying cause is common to both peculiarities, and thus constitutes evidence of the individual value of the two tests in detecting subclinical defects in the hearing organ.

tion of the material. It is impossible on the basis of earlier data to draw a boundary line between what can be regarded as the normal range and an abnormality and for the same reason as has been given for the hearing thresholds. It was therefore necessary to examine more closely the occurrence of elevated reflex thresholds in persons with normal hearing.

The means and ranges for the reflex threshold of the 200 ears in 100 control subjects with normal hearing—50 men, 50 women—are reported in Fig. 3. The results are largely consistent with earlier experience.

On the basis of the data in Table 3 a criterion for the pathologic limit for the reflex threshold has been formulated.

Because of the relatively greater range of the reflex threshold values for 125 and 4000 Hz (these were excluded from the calculations. For the remaining 6 frequencies (250–3000 Hz) the hearing level chosen as first pathologic reflex threshold value was the next 5 dB step above the  $P_{90}$  value for the relevant frequency. This necessary escalation to the attenuator stage used in practice means that the first pathologic value will lie at a statistical level corresponding on average to the 94th percentile. The pathologic limit so established (= the value for the first pathologic reflex threshold level) is shown in Fig. 3.

For a subject to be classed as pathologic with respect to the reflex thresholds the pathologic limit should be reached at one ear for 4 of the 6 test frequencies or at both ears for 2 of them. This criterion was satisfied by 2 men (4 per cent) and 1 woman (2 per cent) in the normal series.

### CONCLUSIONS OF THE RESULTS

In the analysis of the results of the hearing tests the parent group was divided into two sub-groups according to age. The 15 pairs comprising the younger group had a mean age of 33.2 and 30.3 years for the men and women respectively; the corresponding ages for the 15 older pairs were 52.5 and 48.3 years.

The presence of threshold dips in accordance with the criteria is shown in Table 1. They occurred bilaterally in one subject of the control group.

TABLE 3 Median 90th percentile and first pathologic level of reflex threshold

Values given in dB hearing level (ISO)

Frequency	125	250	500	1000	1500	2000	3000	4000 Hz
Median	6.3	81.2	87.4	85.6	90.5	83.5	82.8	90.7
$P_{90}$	85.4	91.0	94.8	93.3	97.3	93.0	93.1	101.0
First pathologic level	—	95	95	95	100	95	95	—



however that the stipulation of subjectively normal hearing as a criterion for the hereditary series also is matched by an audiometrically normal hearing acuity age and sex taken into consideration.

The disadvantages of including older parental pairs had to be weighed against the obvious advantages: the older group would have had more children, and the hearing of both parents and children could be followed over a longer period. The fact that the parents have had more than one deaf child and that no exogenous cause of the defect can be established is a most reliable indication of genetic defect. A long term study of the child's hearing impairment may provide valuable information on this point. A distinctive feature of certain genetic hearing defects is its progressive nature. The progress can be slow or with long intervals and a long follow-up period may thus be required for any decision to be possible. In the present study 13 of the children with measurable hearing remnants could be followed for more than a decade. In 10 of them the impairments were progressive.

The major difficulties of classifying a hearing defect as definitely familial and genetic on the basis of the history and the results of examinations have been dealt with in the Introduction. This is not the place for a detailed account of all the factors on which the final decision for each family was based. suffice it to state that every effort was made to rule out, so far as our knowledge permits, the possibility that the impairment was other than hereditary. Despite this it is possible even probable, that in one case or another an error of judgement might have been made and that the defect was, in fact, of a so far unknown exogenous nature but these cases will be so few as not to jeopardize the validity of results for the group as a whole.

One peculiarity found to occur disproportionately often in the hereditary series was a small but quite distinct dip in the otherwise normal hearing threshold. The dips are situated below 3000 Hz, an area considered not to be vulnerable to exogenous agents. To judge from the approximately similar distribution between the younger and older groups the dips seem to be independent of age. On the other hand, in a few cases followed over a long period some increase in the dip amplitude was found.

To be regarded as significant the dip should meet certain minimum requirements as to its depth and width. Apart from the significant dips the hearing thresholds of other parents contained a number that did not fulfil the criteria. Even if these are included the total is hardly overwhelming.

As evidence of a genetic hearing defect the dip is however most important for other reasons. In sensory-neural hearing impairment of unexplained origin that affects young and middle-aged persons a surprisingly large proportion has a basin-shaped audiometric appearance with the centre in the same area as the dips. These defects are often bilateral and a careful analysis will often disclose a high incidence of deafness in the family.

Another point that indicates that this area of the hearing range is

On the basis of our present knowledge it seems that the only explanation one can offer for the presence of these two peculiarities is that they are endogenous. They satisfy the criteria for what we define as subclinical defects: namely (i) their carriers are unaware of them and (ii) their subtle nature renders them difficult if not impossible to detect with any but refined tests.

### DISCUSSION

As is seen from the analysis, there was a disproportionately high incidence of certain peculiarities in the hearing and reflex thresholds in the parent group with a genetic background of deafness: peculiarities of such a nature that they cannot be ascribed an exogenous cause.

Perhaps the foremost difficulty encountered in a study of hereditary deafness is to ensure an acceptable selection of families. In this investigation an attempt was made to introduce some measure of randomness in the material by using a group of families residing in a particular geographical area supplemented with new families inserted in the series in the order in which they appeared for consultation irrespective of their domicile. This inevitably incurred some degree of skewness as the geographic group was on average older than the chronologic one. Since however the recorded hearing defects were most evenly distributed between the two groups it is unlikely that the results would be decisively influenced by criteria of selection.

But heterogeneous age distribution leads to other difficulties, especially in an attempt to decide whether a subject's hearing may be regarded as normal for his age. For such comparison earlier studies on presbycusis cannot be used, as these are supposed to exclude all subjects with exogenous or endogenous impairment so as to isolate the hearing loss component ascribed to the aging processes only. So far as the parents are concerned it is reasonable to assume that considered as a group they were exposed to the effect of exogenous factors to the same extent as the average individual and with a loss in hearing acuity increasing over the years.

For this reason it was chosen to evaluate the parents' hearing thresholds against the results of the Wisconsin State Fair Hearing Survey (Glorig *et al.* 1957) in which is given the average hearing acuity in a large series, including also the cases of hearing loss, whatever its cause might have been. The results in this study are reported as median hearing levels for the 500-6000 Hz range as a function of age and sex. On this basis of comparison the hereditary series as a whole had definitely better hearing thresholds than the corresponding categories in the WSFHS. This is somewhat unexpected because about one half of the values should have been located below the median line.

The relatively better hearing acuity recorded in the parent groups is probably fictive and most likely due to the more accurate technique of measurement. The result of the hearing threshold examination shows,

TABLE 4 (Cont.)

Individual	Mode of selection <sup>a</sup>	Parent	Age	Life ring threshold <sup>b</sup>	TI threshold (dB) <sup>c</sup>	Acoustic threshold <sup>d</sup>	Hereditary background <sup>e</sup>	Children <sup>f</sup>		
18	Ge	F	46	-	-	-	-	♀	♀	♂
		Mo	42	-	-	+	-	17	18	10
19	Ch	F	46	-	-	-	-	♀		
		Mo	41	-	-	-	-	6		
20	Ge	F	49	-	-	+	+			
		Mo	43	-	+	+	+	24	20	14
21	Ge	F	49	+	-	-	+	+	♀	
		Mo	46	-	-	-	+	27	22	11
22	Ge	{ F	49	-	-	-	-	♂	♂	
		{ Mo	46	+	-	+	+	26	25	21 13
23	Ge	F	51	-	-	+	-	♂		♂
		Mo	47	-	-	+	+	16	17	15
24	Ge	F	52	-	-	+	+		♀	
		Mo	43	-	+	+	+	19	16	
25	Ch	F	52	-	-	+	+	+	♂	♀
		Mo	49	-	-	-	-	20	18	10
26	Ge	F	54	-	-	-	+		♂	♂
		Mo	52	-	-	-	+	24	21	17 15
27	Ch	F	51	-	-	-	-	♂	♀	
		Mo	57	-	-	-	-	23	14	
28	Ge	F	58	-	-	-	-			
		Mo	54	-	-	-	-	27	21	22 22
29	Ge	{ F	67	-	-	-	-			
		{ Mo	63	-	-	-	-	23		
30	Ge	F	71	-	-	-	-	♂	♂	
		Mo	61	-	-	-	-	32	41	21

Ge Geographic Ch chronologic selection

Bracket indicates that the parents are consanguineous.

Hearing loss greater than median for corresponding sex and age group at more than one test frequency.

Hearing loss greater than 100.

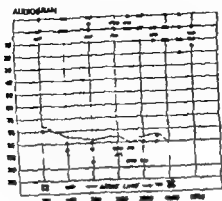
Exceeding the criterion (p. 344).

Hereditary hearing impairment in family if more than one child is deaf or there is consanguinity between the parents, both parents are scored +.

Filled symbol denotes deaf subject; figures in parentheses indicate twins.

TABLE 4 *Summary of findings relating to the hereditary material*  
 Families arranged in order of the father's age

Family no	Mode of selection	Parents <sup>a</sup>	Age	Hearing threshold <sup>c</sup>	Threshold dip <sup>d</sup>	Reflex threshold <sup>e</sup>	Hereditary background	Children <sup>f</sup>
1	Ch	Fa	21	-	-	+	+	
		Mo	22	-	-	+	-	3
2	Ch	{ Fa	22	-	+	-	+	♀
		{ Mo	23	-	+	+	+	3
3	Ch	Fa	28	-	+	-	-	♂
		Mo	22	-	-	+	-	3 2
4	Ch	Fa	31	++	-	-	-	♀
		Mo	29	-	+	+	-	9
5	Ch	Fa	32	-	-	-	-	♀
		Mo	29	-	+	+	-	5 1
6	Ch	Fa	32	-	-	-	+	
		Mo	29	-	-	+	+	7 4
7	Ge	Fa	33	+	-	-	+	♀ ♀ ♀
		Mo	30	-	-	-	-	12 11 6
8	Ge	Fa	33	-	-	+	+	♀
		Mo	34	+	+	-	+	15 11
9	Ge	Fa	35	-	-	-	-	♂ ♀
		Mo	35	+	-	+	+	7 6
10	Ch	Fa	36	+	-	-	+	♀
		Mo	29	+	-	-	+	10 6 5
11	Ch	Fa	36	++	-	+	-	♀
		Mo	26	+	-	+	+	3 1
12	Ge	F	39	-	-	+	+	♀ ♂
		M	40	+	-	-	+	15 15 9
13	Ch	Fa	40	-	-	+	+	♀
		Mo	28	-	-	+	+	9 6
14	Ge	Fa	40	-	-	-	-	♂ ♀
		M	39	-	-	+	+	13 12 10 6
15	Ch	Fa	40	-	-	+	+	
		Mo	39	-	-	+	+	14 12
16	Ch	Fa	44	++	-	+	+	♀
		Mo	37	-	-	-	+	6 3 1
17	Ch	Fa	45	-	-	-	-	♂
		Mo	40	-	-	+	-	11 6



particular susceptible to genetic defects is that a similar centre of impairment has been found in cases of Turner's syndrome. The underlying genetic cause here is sex-chromosome aberration. In more than 40 per cent of these patients such dips or a basin shaped threshold pattern, centered in the same frequency range, were found (Lindsten 1963, Anderson *et al.*, 1968).

It is rewarding to examine this particular location of the impairment in the frequency range of hearing in connection with certain earlier physiologic and histologic observations. The perception of the frequency range in question involves quite a small section of the basilar membrane comprising the upper part of the basal turn and the lower part of the second. If it is assumed that the observed peculiarities of the hearing thresholds of the hereditary series have their origin in the cochlea, the defect should be situated in this very part of the basilar membrane. This is a site of damage and an audiometric pattern which are distinctly different from the site of the exogenous defects, where it is the more basal parts that are first affected.

The same point of onset for genetic hearing defects as reported here has also been demonstrated histologically in waltzing guinea pigs (Lurie 1941) and dogs (Anderson *et al.* 1968).

The question why this region appears to be a genetic locus minoris resistentiae can be looked upon in the light of some earlier experimental findings. In normal series of mice (Lorente de No, 1933) and opossum (Larsell *et al.* 1944) it has been found by histologic examination that the embryonic development of the receptors in the organ of Corti begins in this region to continue in the basal and apical direction. Measurements of cochlear microphonics of the developing rabbit support this view (Ånggård, 1965: 106/).

The histologic investigations in animals have shown that the genetic defects in the organ of Corti appeared in the very area in which the embryonic development begins, and that the process of breakdown—atrophy—probably does not begin until the sensory cells are fully or partly developed (Bosher & Hallpike 1960). There are thus a number of facts that indicate that a hearing threshold defect in the middle frequency range of the hearing may be regarded as indication of a genetic defect in the hearing organ.

So far as the search for sub-clinical defects is concerned the stapedius reflex test is in several respects more reliably evaluated than the hearing threshold test. The threshold for this reflex has proved to be very little affected by exogenous factors or age. Even persons where years of exposure to noise combined with presbycusis has resulted in a marked elevation of the hearing threshold may record reflex thresholds within normal limits. In this fact lies the value of the stapedius reflex as a test of recruitment. The effect of exogenous damage on the hearing threshold is unaccompanied by any effect on the reflex threshold and the resulting reduction in the gap between the two thresholds is assumed to indicate recruitment. Only



hold decay or impaired loudness function. There is thus more evidence for than against a cochlear localization, an opinion further supported by the above argumentation regarding the probable origin of the threshold dip. It present a series of experiments is carried out to penetrate this problem.

It is a major step forward to be able, by two simple tests, to identify at least some of the normal hearing carriers of hearing defects. This is of considerable clinical value in ascertaining the aetiology of deafness among children belonging to the large "unknown" group and also of great interest for the further study of the mode of inheritance of the recessive hearing defects.

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#### ZUSAMMENFASSUNG

Da die meisten Träger von Erbanlagen rezessiver Schwerhörigkeit nicht in stärkerem Masse Hörstörungen zeigen als die Durchschnittsbevölkerung ist es nicht möglich derartige Erbräger mit üblicher Routine-Audiometrie zu identifizieren. In der vorliegenden Untersuchung wurde nun versucht mit speziellen Testmethoden und zwar mit Hilfe von Békésy Audiometrie und der Schwellenbestimmung des Stapedius-Reflexes, etwaige subklinische Besonderheiten des Gehörs aufzudecken. Das Untersuchungsmaterial bestand aus einer Gruppe von 30 Elternpaaren mit normalem Gehör bei denen eine starke Indikation zu erblicher Schwerhörigkeit vorlag. Sie hatten insgesamt 74 Kinder von denen 47 eine schwere erbliche Hörschädigung oder totale Taubheit zeigten. Beim Vergleich mit einer normalhörenden Kontrollgruppe konnten in der Gruppe der 30 Elternpaare zwei Besonderheiten in den audiometrischen Befunden festgestellt werden, nämlich kleine aber deutliche Dips im mittleren Frequenzbereich der Hörschwellenkurve und abnormal hohe Schwellenwerte für den akustisch ausgelösten Stapedius Reflex. Anschliessend werden die Beobachtungen im Zusammenhang mit früheren genetischen und histologischen Befunden näher diskutiert.

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It is a major step forward to be able, by two simple tests, to identify at least some of the normal hearing carriers of hearing defects. This is of considerable clinical value in ascertaining the aetiology of deafness among children belonging to the large unknown group and also of great interest for the further study of the mode of inheritance of the recessive hearing defects.

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## POLYTOME PANTOPAQUE A TECHNIQUE FOR THE DIAGNOSIS OF SMALL ACOUSTIC TUMORS

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Fortunately the day is past when our diagnostic capability was limited to the recognition of patient with advanced tumors who presented with multiple cranial neuropathy and increased intracranial pressure. In no small measure this has been due, in recent years, to advances in the recognition of these tumors by positive contrast material. The polytome pantopaque study is an extension of this work and has allowed an accurate assessment of those patient with small tumors presenting with minimal neurologic and otologic complaints in whom the diagnosis of acoustic tumor is suspect.

The adaptation of microsurgical techniques to the removal of acoustic tumors has made the diagnosis of the small acoustic neuroma more than an academic exercise. The removal of these tumors is now possible with a minimum of neurologic morbidity. This has been emphasized by every recent series in both the otologic and neurosurgical literature (House, 1964; 1966; Pool, 1966; Olivecrona, 1967; Drake, 1967).

Before treatment may be undertaken, however, an accurate diagnosis must be made. It is the purpose of this presentation to outline a technique which the authors have found invaluable in the diagnosis of small acoustic tumors. This technique, which we call a polytome-pantopaque study, combines the use of a small aliquot of Iophendylate (pantopaque), plain radiographs, and polytome x rays.

### *The patient with the small acoustic tumor*

The complaint of unilateral hearing loss, tinnitus, unsteadiness, or vertigo is usually a symptom that causes these patients to seek medical advice. Unfortunately the audiological findings in such a patient may be variable (Johnson & Sheehy, 1966). The pattern of hearing loss on the audiogram may be minor and can occur at any frequency range. Occasionally the audiogram may be normal. The ability to discriminate the meaning of words is usually impaired to a more marked degree than responses on the plain audiogram, but like the latter may also be normal. Responses of the

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Fig. 1 Antero-posterior polytome x-ray through the internal auditory canals. Note bulbous enlargement of the canal on the left. A large air cell is seen over the superior lip of the canal on the right.

labyrinth to caloric stimulation may be normal and are more often hyporeactive than completely inactive (Hitselberger 1967).

On neurologic examination, decreased facial sensation, facial paresis, and cerebellar ataxia are not seen in this group of patients. The only consistent neurologic finding has been decreased sensation along the posterior aspect of the external auditory canal (Hitselberger 1966). This is believed to be due to pressure by the tumor on the sensory portion of the facial nerve in the internal auditory canal. Even this finding may not always be present in the patient with a small acoustic tumor.

Carefully taken petrous pyramid x-rays using the Stenvers, Chamberlain, Towne, and Caldwell views are an important part of the workup. Differences of as little as 1 mm between the diameter of the internal auditory canal of the two sides may be of diagnostic significance (Crabtree & House 1964).

#### *Polytome pantopaque*

The fluoroscopic iophendylate study of the posterior fossa has proven to be an excellent examination for those patients harboring larger cerebello-pontine angle tumors (Scanlan 1964). In comparison with pneumoencephalography this examination has been more accurate and associated with less discomfort to the patient. We have not been satisfied, however, with the results of this test when dealing with smaller tumors because of the necessity for orientation of the contrast in relation to the surrounding bony landmarks of the internal auditory canal.

Polytomography allows the taking of 1 mm x-ray sections through the petrous pyramid in almost any direction (Compere & Valvassori 1964; Mundnich & Freg, 1959). By itself this has been an extremely valuable addition to the radiologic armamentarium because we are able to detect



FIG. 2. Position of patient on X-ray table prior to exposure of polytomograms. Tilt of the table downward allows the contrast material to gravitate into the posterior fossa, flooding the cerebellar pontine angle and internal auditory canal.

changes in the internal auditory canal and meatus that would not be observed on the conventional plain films (Fig. 1). Large air cells that obscure the internal auditory canal may be delineated. The exact length of the entire canal, as well as the associated structures of the inner ear can be clearly defined.

We have combined polytomography with the use of contrast material in the subarachnoid space. This has allowed us to see both the important bony structures around the internal auditory canal and the tumor outlined by contrast material. This has been especially valuable in the case of small tumors confined to the canal or only slightly protruding into the posterior fossa. In the past these tumors have been inadequately outlined by both pneumoencephalography and lophendylate cisternography.

#### *Technique of Study*

The examination is undertaken only after otologic, neurologic, and plain X-ray evaluation have indicated the possibility of an acoustic tumor. Preliminary sedation has not been used. One cc of lophendylate (pantopaque)



FIG 3 Patient has been returned to horizontal position and turned prone. The head is positioned so that the involved petrous pyramid is parallel to the x-ray plate

is introduced into the lumbar subarachnoid space under sterile conditions using a no. 24 spinal needle. A 1 cc specimen of spinal fluid is withdrawn for protein analysis. The small bore of the spinal needle results in only a minute opening in the dura and arachnoid and does not impair the introduction of iodized oil into the subarachnoid space.

After the introduction of the contrast material the patient is placed on the x-ray table in the lateral decubitus position with the involved side down. The shoulders are firmly secured. The table is tilted downward in a cephalad direction approximately 35° (Fig 2). This position allows the contrast material to run up the lateral gutter of the spinal canal into the posterior fossa, flooding the cerebellopontine angle and internal auditory canal. The patient is allowed to remain in this tilted position for approximately three minutes so that the iophendylate will migrate upward. The table is then returned to a horizontal position and the patient is turned prone. The head on the involved side is positioned so that the petrous pyramid is parallel to the x-ray plate (Fig 3). A plain Stenvers view is exposed at this time. In most instances, the tumor will be delineated by this plain radiograph. The patient's head is then fixed in position and a series of polytome x-rays are exposed through the internal auditory canal.



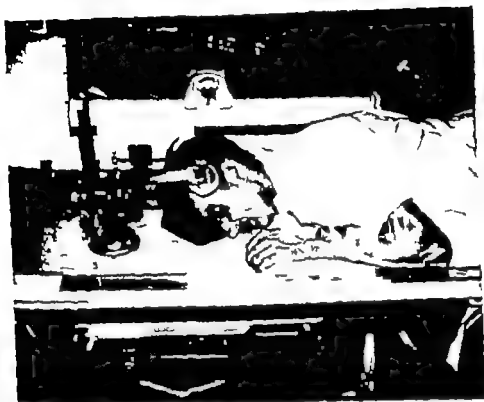


FIG. 4. Fixation of head during exposure of the polytome x-rays.

(Fig. 4) After exposure of the polytome x-rays and the plain radiograph, the contrast material is transferred to the opposite uninvolved side. This is accomplished by hyperextending the patient's head and rotating 135° so that the petrous pyramid of the uninvolved side is placed parallel to the x-ray plate (Figs. 3 and 6). A set of polytome x-rays are exposed on this side completing the examination. No attempt is made to remove the small amount of iophendylate (1 cc) (Figs. 7 and 8).

#### COMMENTS

This technique is adapted to tumors confined to the internal auditory canal or only slightly protruding into the posterior fossa. The incidence of post-procedural headache, back and leg ache have been less than 5% of over 200 patients. It should be stressed that a small aliquot of contrast material be used, and that this material be placed in the subarachnoid compartment with a small bore (no. 24) needle.

Two complications in this series have prevented filling of the internal auditory canal and cerebellopontine angle.



FIG 5 Transfer of contrast material to the opposite side is accomplished by hyperextending the patient's head and rotating 135°

- 1 Large osteophytes or hypertrophic disc changes along the spinal axis may prevent the contrast material from entering the posterior fossa. In this situation turning the patient supine will allow the contrast material to collect in the posterior fossa.
- 2 If the contrast material is instilled in the extra arachnoid space it will not move and re-injection is necessary.

The polytomic pantopaque study is not recommended for tumors that are felt to be of moderate or large size since the area that can be covered by the polytomic field is limited. In those patients having Vth nerve abnormality in association with deficits in the VIIth and VIIIth nerves, the conventional fluoroscopic pantopaque study will usually delineate the tumor quite satisfactorily since these tumors tend to be larger.

The value of the plain radiograph in association with a small aliquot of iophendylate should be stressed. In most instances, this single view will serve to make the diagnosis of an acoustic tumor (Figs. 9 and 10).

Hardy & Crowe in 1936, after a detailed study of 250 temporal bones from consecutive autopsies found four histologically verified acoustic tumors. These arose deep within the internal auditory canal from the



FIG. 6. The petrous pyramid of the opposite side is positioned parallel to the x-ray plate

vestibular portion of the VIIIth cranial nerve and had been overlooked at the time of the initial postmortem examination. The largest of these tumors was 2.5 cm in diameter. In the past, it was believed that acoustic tumors occurred infrequently and constituted only 5 to 10% of all brain tumors. It is our feeling that the incidence of this tumor is much higher. The long ignored work of Hardy & Crow would tend to substantiate this view.

### ZUSAMMENFASSUNG

Verfahren zur radiologisch-nachweisbaren Darstellung von Geschwülsten innerhalb des inneren Gehörganges, oder bloss leicht in die hintere Schädelgrube ragend. Eine kleine Menge (1 cc) von Kontrastmaterial, mit dem Polytom-Röntgenapparat ergibt klares Bild. Entsprechend Lagerung des Kranken leitet das Kontrastmaterial, durch Schwärzen, aufwärts in den Kleinhirn-Brückenwinkel. Eine kleine Führe in der Seitenprojektion und in Fluoroskope wird die Geschwulst gut abgegrenzt.

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FIG. 7. Normal polytome pantopaque study of the internal auditory canal. Note the contrast above and below the crista (arrow) at the lateral end of the canal.



FIG. 8. Abnormal polytome pantopaque study of the internal auditory canal. The medial border of the tumour is filled by the contrast material. The tumour is protruding slightly into the posterior fossa.



FIG. 9. Plain Stenver's projection X-ray in association with small aliquot (1 cc) of contrast material. Small tumor is clearly outlined protruding from the left internal auditory canal.



FIG. 10. Larger tumor outlined by small aliquot (1 cc) of contrast material.

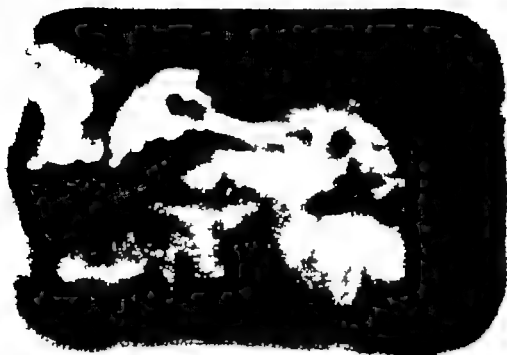


FIG. 7 Normal polytomographic study of the internal auditory canal. Note the contrast above and below the crista falciformis at the lateral end of the canal.



FIG. 8 Abnormal polytomographic study of the internal auditory canal. The medial border of the tumor is filled by the contrast material. The tumor is protruding slightly into the posterior fossa.

## SURGERY IN PROFOUND HEARING LOSS

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Results are reported in 7 adult cases with profound deafness. Six of them were found on tympanotomy to have otosclerosis and improved after stapedectomy. Tympanotomy was also made on 37 Deaf School pupils who had a similar pattern of hearing, i.e. a severe air conduction loss but some response by bone conduction. Fifty-one per cent of the latter improved by an average of 10 dB or more when tested one month post-operatively. One year later only 1 per cent retained their improvement. It is concluded that all profoundly deaf adult cases responding to some bone-conducted sound should be explored. Of children, however, only those with bone conduction hearing up to 2000 cps are suitable candidates for tympanotomy.

Surgery in cases of advanced hearing loss due to stapes fixation has been greatly facilitated by the oval window approach. Exploratory tympanotomy—although a minor procedure—provides definite information on possible middle ear pathology. Hearing may be brought up to the level of maximal cochlear capacity through preservation or reconstruction of the ossicular chain.

Sheehy (1962) recently reported on 13 cases of far advanced otosclerosis in 3 patients the hearing level was in excess of 85 dB, in 12 there was no response to air conduction, and none responded to audiometer bone conduction. Tympanotomy was made in a total of 26 cases; in 5 the middle ears were without pathology.

Obviously in such cases hearing can only rarely be improved to the extent of enabling the patients to discard their hearing aids. However, it may improve so much that the patients can use their aids more efficiently than before. This was the main finding in Sheehy's 13 cases, including also 2 in which there was no response to air- and bone-conducted sounds pre- or post-operatively.

This study was initially confined to profoundly deaf adults with suspected otosclerosis and extended to include those pupils of the Oulu School for the Deaf in whom repeated hearing tests pointed to a conductive component. For this purpose 37 deaf children (6 between 7 and 10 years of age, 21 between 11 and 15 and 10 over 15 years) were chosen. The original series of profound hearing loss in adults consisted of 7 persons.

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TABLE 1 Synopsis of operative results

Total	Frequency range								Changes in frequency range				Changes in threshold db				Operative findings	Operation
	Highest frequency heard								1 month <sup>b</sup>		1 year <sup>b</sup>		1 month <sup>b</sup>		1 year <sup>b</sup>			
	A.C.	B.C.	A.C. <sup>b</sup>		B.C. <sup>b</sup>		1 month		1 year		1 month		1 year					
											</							

tion. In group II, 2 patients heard the audiometer bone conducted tone at 0 dB setting this also applies to 3 patients in group III (though none heard 2000 cps in group IV the bone conduction response extended to 1000 cps in 2, to 2000 cps in 2, and to 4000 cps in 4 ears.

Operative findings in group II (12 ears) were as follows the stapes was immobilized by a network of adhesions in 6 ears but when these were cut and partly removed the footplate appeared mobile. In 5 ears the posterior end of the footplate resisted pressure when its mobility was being tested 2 ears were subjected to total and one to partial stapedectomy and the remaining 3 ears to simple mobilization in one case there appeared no tympanic pathology.

In group III, adhesions were removed in 3 ears and the footplate was found mobile in 7 there was restricted movement stapes mobilization was performed in 2 of them partial stapedectomy in 2, and total stapedectomy in 3. On tympanum was normal.

Group IV included 3 ears with adhesions and 11 in which the footplate did not move normally. Simple mobilization resulted in good movement in 4 cases, partial stapedectomy was made in 3 and total stapedectomy in 4 ears.

In the whole series of 39 ears, bony footplate fixation of otosclerotic type was 1 and in 2 cases only. The fixation in all others created the impression of fibrous resistance at the footplate margins.

### *Testing Procedure*

Standard audiometric air and bone conduction and speech tests were carried out at intervals to ascertain accuracy. Loading a special bone vibrator with increased voltage was also used in many cases. In addition 256 and 512 cps tuning forks were used to obtain qualitative data. Anyone not responding to bone conduction for these two forks was considered unsuitable for tympanotomy. All patients were tested when leaving the hospital one month postoperatively and after one year.

### *Surgical Technique*

An endaural tympanotomy was made with sufficient annular bone removal and the oval window region examined. If adhesions were found, these were carefully cut, often simultaneously with the stapedius tendon and the mobility of the ossicles and of the footplate was tested. In the presence of a mobile chain nothing further was done. If the footplate was felt to be fixed, it was either mobilized or removed (in part or totally). If removed *in toto* the window was sealed with fascia and a polythene tube or stainless steel wire inserted from the incus to the graft.

#### *Adult cases*

The preoperative average hearing levels at 500, 1000 and 2000 cps exceeded 90 dB by air conduction in all cases. In one the highest frequency heard was 500 cps, in one 1000 cps, in one 2000 cps while in four hearing extended to 4000 cps. By bone conduction all patients responded to tuning forks and heard at least the low frequencies at the maximum audiometric setting.

In 8 cases there was footplate fixation and stapedectomy was done. The hearing gain varied in 5 cases from 34 to 70 dB. One patient with hearing up to 1000 cps obtained a 20 dB improvement and could start using a hearing aid. In the seventh case, with hearing only at 250 and 500 cps, there was advanced tympanosclerosis, and a mobilized footplate was connected to the drum by means of a polythene strut. The frequency scale widened from 500 cps to 4000 cps and the average level was 84 dB.

These cases are presented as group I in Table 1. It is seen that both the average improvement and the widening of the frequency scale were maintained.

#### *Children*

The patients were divided into three groups according to the preoperative range. In Table 1 group II consists of 12 ears in which the highest frequency heard was 500 or 1000 cps, group III of 13 ears with an upper limit of 2000 cps, and group IV of 14 ears with hearing up to 4000 cps. The patients in all groups responded to  $C_1$  and  $C_2$  forks by bone conduc

This favourable result, however, was not maintained: only 15 per cent of those initially improved retained their gain after one year.

The cause of the lost gain is not clear. We think that in the majority of our cases there was a small conductive component which was temporarily eliminated in the cases with numerous adhesions. Since no steroids were used after operation, it is possible that, similarly as in routine stapedectomies, a number of new adhesions developed postoperatively. Another factor seems to be that ligament fixation was the main pathology: mobilization, making the ligament temporarily more yielding, resulted in improved function. In cases treated by total stapedectomy, however, none of the above factors should cause a subsequent loss of the gain. Nor can cutting of the stapedius tendon be a cause of either the initial improvement or later deterioration at these high intensity hearing levels. All children had also been tested on so many occasions that errors due to their inability to perform the test are not likely.

In profoundly deaf adult patients tympanotomy seems fully justified if otosclerosis is suspected. Bone conduction testing with 312 cps fork is generally reliable, whereas the 256 cps fork may cause confusion because its mechanical vibrations are felt on the skull. In children, however, the final percentage of improvement is so low that tympanotomy should only be made if there is amplified audiometric bone conduction hearing up to 2000 cps at least. In the less favourable cases it is probably preferable to perform tympanotomy in adult age when the proliferative tissue response is less marked.

#### ZUSAMMENFASSUNG

Sieben Erwachsene wurde wegen eine sehr schweren Hörverluste (über 90 dB) operiert. Otosklerosis wurde in 6 Fällen gefunden, mit Hörgewinn nach Stapediomi. Tympanotomie wurde an 37 Kindern. In Taubstummenschule durchgeführt, deren Hörverluste dieselben F rmen zeigten wie die Audiogramme von Erwachsenen. Bei Kindern wurde eine Verbesserung von 10 dB oder mehr in 1 nach einem Monat festgestellt. Mit doch zeigten nach einem Jahr nur 15% dieser Fälle in permanent Verbesserung. Fast laube Erwachsene mit Gehör nur in Knochenaufleitungstöne sollten operiert werden. Kinder dagegen sollten Knochenleitungshören wenigstens bis 2000 Herz haben, bevor in Tympanotomie indiziert ist.

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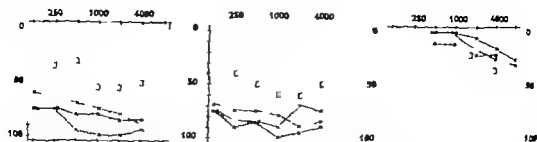


FIG. 1 Three children's ears with hearing improvement over one year's period. The preoperative air conduction curves (continuous line) for both ears and the postoperative curve (broken line) for the operated ear together with the preoperative bone conduction are shown.

Results one month postoperatively showed that, in group II 3 out of 12 ears had improved by 10 dB or more in group III 7 out of 13 ears, and in group IV 8 out of 14. This improvement was also noticed by the patients themselves and by the teaching staff. In the test made one year postoperatively however only 3 of the initially improved 20 ears retained their gain. These cases are presented in Fig. 1.

Histologic examination of the removed pieces of stapes footplate was made in 8 cases. There were signs of cartilaginous degeneration and fibrotic changes in most, but definite otosclerotic foci were present in none.

Widening or narrowing of the frequency range following operation occurred in all groups. One year after operation 3 of the ears were 10 dB worse than preoperatively. This change was also noted in the contralateral ear in 2 cases and was obviously not due to operation.

## DISCUSSION

Despite the many similarities in audiometric pattern between the adults and children these 2 groups differ in one respect while the former had heard better when young the latter had always been hard of hearing. In selecting suitable candidates for operation therefore anamnestic data should be carefully considered.

This does not imply that otosclerosis might not start in infancy. For instance Whetnall (1953) had in her series 17 hard-of-hearing children with parental otosclerosis, the hearing loss being subtotal in 2. Ten years ago, the senior author restored hearing to both ears of a young man who had been deaf from otosclerosis since infancy.

In the adult group with 6 otosclerotic ears, one improved from 96 to 26 dB, the other 5 improved to or near the level of preoperative bone conduction. The change from profound deafness to moderate hearing loss however allowed full rehabilitation with some additional amplification.

The results in the group of children seemed very encouraging at first. 20 cases out of 39 (51 per cent) showed improvement of 10 dB or more

tions, there has been an interval of at least 2 minutes. Normally the caloric test is performed without the use of Bartels glasses. If however no nystagmus was seen, we applied the glasses to secure detection of even the weakest reactions. The duration of the nystagmus was registered, and we found that in every case with reaction (with or without the glasses) the nystagmus lasted for more than 80 seconds. This is the reason for the below mentioned classification of the intensity of the caloric reactions in which the duration of the nystagmus is not used.

## RESULTS

We have grouped the findings in 5 categories

- (1) Normal reaction reaction without Bartels glasses as well at 30 °C as at 44 °C.
- (2) Reduced reaction reaction at 30 °C. At 44 °C only reaction with Bartels glasses or no reaction at all at this temperature.
- (3) Markedly reduced reaction no reaction at 30 °C or at 44 °C, but reaction at 20 °C.
- (4) No reaction no reaction at 20 °C.

In Table 1 is shown the results according to this classification

We have grouped the children in 3 categories, according to the etiology of the deafness, using the classification of Sandberg & Terkildsen (1965) see Table 2

(a) Anamneses non-contributory Among the 36 children belonging to this group, the deafness of 15 is caused by hereditary factors, and it is probable that this is also the case in the majority of the rest.

(b) Prenatal origin in all 7 cases, maternal rubella in the first trimester was registered.

(c) Perinatal origin in one of the cases, a severe asphyxia is the probable reason, the other was a case of erythroblastosis

(d) Postnatal origin one case of labyrinthitis, one of encephalitis, and 4 cases of meningitis.

(e) Non-classifiable origin cases with several possible explanations of the deafness, in which no distinction is possible.

TABLE 1. Results of the caloric test in 83 patients (110 ears).

Normal reaction	17	(15)
Reduced	38	(34)
Markedly reduced	5	(4)
No reaction	30	(27)
Total (ears)	110	(100)

TABLE 2. Classification of the etiology of the deafness.

Non-contributory	36
Prenatal	7
Perinatal	2
Postnatal	6
Non-classifiable	4
Total	55

## DIFFERENTIAL CALORIC REACTIONS IN DEAF CHILDREN

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Material from 55 totally deaf children is presented. The vestibular function has been examined by means of a differential caloric test, using the Hallpike-Fitzgerald method. The results are compared with the etiology of the deafness and the changes found at tomography. The results appear to differ from earlier findings, as only a few reveal normal reactions. The discrepancies are discussed and it is concluded that a rather close relation exists between hearing impairment and vestibular function.

Previous papers on the vestibular function in deaf or hard-of-hearing patients are based upon different methods of examination, and consequently not directly comparable. Sandberg & Terkildsen (1965) published an extensive survey on the literature, and examined the vestibular function in 57 children from a school for severely hard-of-hearing by means of the Hallpike-Fitzgerald method. Applying the same technique, we have examined a similar number of children from the State School for Deaf Children in Copenhagen. The two materials should make it possible to compare the vestibular function in different degrees of hearing impairment.

Our material comprised 55 children, 0-15 years old, all totally deaf. Apart from having their vestibular function examined, tomography of the temporal bones has been performed.

### METHOD

Prior to the caloric test otoscopy was performed in order to secure normal ear drums. One patient with bilateral perforation was excluded from the material. Furthermore the patients were examined regarding spontaneous and positional nystagmus, which was found in 2 cases. These patients were also excluded from the material.

Both ears were irrigated with water at 30°C for 40 seconds. In case of reaction the irrigation was repeated at 44°C also for 40 seconds. In cases of no reaction at 30°C, the ear was irrigated at 20°C for 2 minutes (Kristensen 1954) and if any reaction occurred at this temperature, the stooping test was performed. If it is a true caloric reaction, the nystagmus will change its direction after tilting the head forward. Between the irriga-

remnant of hearing the child is referred to a school for severely hard-of-hearing from which the material of Sandberg & Terkildsen comes. They were able to classify the children in 3 groups according to the hearing, and yet they titled the paper "caloric tests in deaf children." We recommend that the word deaf be used exclusively in cases of no hearing.

As mentioned, we—as did Sandberg & Terkildsen in some of their cases—used Bartels glasses in cases where no nystagmus was seen, or in cases with doubtful reactions. In all the reactions of 39 ears were studied that way. Thirty-seven of these ears were placed in the group "reduced" and 2 ears in the group "markedly reduced." In the latter the reactions at 20 were doubtful and the patient would have been placed in the group "no reaction" if the glasses had not been used. Application of the glasses in the 37 ears now termed reduced has only influenced the relation between the groups of reduced and markedly reduced reactions, and has not unduly diminished the group of no reaction.

Our results (Table 1) differ somewhat from other authors. Sandberg & Terkildsen found 57% with normal reactions. Of the same dimensions are the findings of Shambaugh (1930) Lindenow (1945) Arvig (1945) and Everberg (1961) whereas we found only 15% with normal reactions. If however we compare our results with the findings in the group with the poorest hearing (more than 98 dB) of Sandberg & Terkildsen's material, there is almost total agreement: 19% with normal reactions to our 15% and 23% with no reaction to our 27%. As to the disagreement with the findings of the other mentioned authors, several explanations are possible. Partly the methods are not identical with ours, apart from Everberg's, whose material on the other hand, is different from ours, and partly there is no detailed information about the hearing. As just shown, there is a close relation between the degree of the hearing impairment and the vestibular function, and it is highly probable that the average hearing in the other materials is better than in ours, and thus explaining the discrepancies between the findings. Everberg (1961) states that partial loss of vestibular function in connection with deafness is rare. This we have not been able to confirm, as we in 85% of the cases find a more or less reduced activity of the vestibular organ.

In Table 2 a comparison between the etiology of the deafness and the vestibular function is made. It is interesting that the prenatal group which exclusively comprises cases of prenatal rubella, no cases of severely impaired vestibular function are recorded. This is in accordance with the findings of Sandberg & Terkildsen and Arvig. In accordance with Lindenow are the findings in the cases of postnatal, i.e. acquired deafness, among which there are no cases with normal vestibular reactions.

Table 4 gives a comparison between the radiological findings and the vestibular function. Some of the findings are published (Jensen, 1967) and the rest will be published in detail later. It is seen that while the relative amount of cases with normal function is the same in the 2 groups,

TABLE 3 *Comparison between the etiology of the deafness and the vestibular function*

	Prenatal	Perinatal	Postnatal	Non-control- butory	Non-classi- fiable	Total (ears)
Normal reaction	5	1	0	7	4	1
Reduced	0	1	5	43	0	58
Markedly reduced	0	0	0	3	2	5
No reaction	0	2	7	19	2	30
Total (ears)	14	4	12	72	8	110

TABLE 4 *Comparison between the radiological findings and the vestibular function*

	Tomography normal	Tomography pathological	Total (ears)
Normal reaction	11 (1 %)	6 (16 %)	17
Reduced	41 (90 %)	14 (36 %)	58
Markedly reduced	2 (5 %)	3 (12 %)	5
No reaction	17 (20 %)	13 (36 %)	30
Total (ears)	74	36	110

In Table 3 the vestibular function is compared with the etiology of the deafness.

As mentioned tomography of the temporal bones has been performed in all the children. In 20 of the patients (36 ears) some sort of pathological changes of the inner ear was found. In 34 of these ears, the findings must be considered as congenital malformations of either the cochlea or the vestibule/semicircular canals, or both. In one patient osseous obliteration of the entire labyrinth due to labyrinthitis was found. Table 4 is a comparison between the radiological findings and the vestibular function.

## DISCUSSION

The pupils at the State School for Deaf Children in Copenhagen are nowadays totally deaf. They are referred from the State Hearing Center Copenhagen, which only refers children without any useful remnants of hearing. They do not respond to shouting and the audiograms show in only a few cases any remnants of hearing at or above 1000 Hz. Below 1000 Hz, there are none with a hearing better than 80 dB. Moreover, it is probable that the obtained audiograms in most of the cases is only a manifestation of sense of vibration and not an expression of any real hearing.

According to Everberg (1961) the term 'deafness' is not well-defined. He advocates the use of the word only in cases where no hearing is left, and we feel it justified to apply the term on our material in cases of any



## THE ACOUSTIC MIDDLE EAR REFLEX IN UNANESTHETIZED RABBITS

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It is demonstrated that the response of the acoustic middle ear reflex can be recorded in awake rabbits by measuring the change in the acoustic impedance in a way similar to what has been done in man. The excitability of the reflex was measured in the frequency range between 500 and 3000 cps. The reproducibility of the measurement in the same rabbit is in the order of 3 dB over a period of one month, whereas there is a considerable individual variation. It was found that the excitability of the reflex is slightly higher when activated by ipsilateral than by contralateral stimulation. It was further shown that the reflex exhibits no appreciable fatigue during 1 minute stimulation with a 2000 cps pure tone.

Anesthetized animals have frequently been used in studies on the function of the middle ear reflex although it is known that the anesthesia affects the reflex. In some studies anesthetics have been avoided and decerebrated or decorticated animals have been used instead (Lorente de No, 1933; Wersäll 1958). Although the effect on the middle ear reflex of decerebration or decortication may not be as severe as anesthesia, it can not be taken for granted that the function of the reflex is the same as in an unanesthetized normal animal.

In most studies on the activity of the middle ear muscles in unanesthetized animals implanted electrodes have been used either in order to record the action potentials of the two muscles individually (Bornachstein & Krejci, 1952; Wersäll 1958; Salomon, 1966) or in order to record changes in the cochlear microphonic potential (Galambos & Rupert, 1959; Simmons, 1959, 1962, 1964; Hilding, 1966). Recordings of the electrical muscle activity show the relation between the activity of the two muscles but do not provide direct information about the changes in the middle ear's acoustic performance caused by the activity of the muscles. Furthermore, the electromyographic activity in the two muscles may appear before muscle contraction has influenced the acoustic properties of the middle ear. The change in the cochlear microphonic potential on the other hand provides precise information about the net change in sound transmission caused by the activity of the two muscles. Both methods, however, imply chroni-

the group with the pathological tomographic findings comprises more cases of pronounced impaired vestibular function than the group with no radiological changes. In 3 ears a severe malformation of the lateral semicircular canal was found and none of these responded to the irrigation. In the case with bilateral osseous obliteration no function was present.

### CONCLUSIONS

The present investigation confirms the conclusion of Sandberg & Terkildsen that there is a parallelism between hearing loss and vestibular function. Our material consists of children who are totally deaf and this probably explains why we only find 15% with an intact vestibular apparatus, a very low figure compared with earlier findings. It should also be noted that further evidence is given that the vestibular function is not completely extinguished because of prenatal rubella. Finally it is shown that there is no close relation between vestibular function and radiological (osseous) malformations of the inner ear. However it should be noted that in 3 ears with malformations of the lateral semicircular canal no response to the caloric test was found.

### ZUSAMMENFASSUNG

Die Vestibular Funktion wurde mit differential kalorischer Prüfung von Hallpike-Fitzgerald bei 53 tauben Kindern untersucht. Die Ätiologie der Taubheit und die tomographischen Veränderungen werden mit der Vestibular Funktion verglichen. Die Reaktion wird nur in einzelnen Fällen als normal befunden was mit früheren Untersuchungen nicht übereinstimmt, und die fehlende Übereinstimmung wird diskutiert. Daraus folgert, dass eine enge Verbindung zwischen Vestibular Funktion und dem Ausmass der Taubheit besteht.

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Anesthetized animals have frequently been used in studies on the function of the middle ear reflex although it is known that the anesthesia affects the reflex. In some studies anesthetics have been avoided and decerebrated or decorticated animals have been used instead (Lorente de No, 1933; Wersäll, 1958). Although the effect on the middle ear reflex of decerebration or decortication may not be as severe as anesthesia, it cannot be taken for granted that the function of the reflex is the same as in an unanesthetized normal animal.

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cally implanted electrodes which may affect the reflex action. In some animal experiments, finally the tension of the two muscles was recorded with the aid of strain gauges attached to the muscle tendons (Lorente de Nó & Harris, 1933; Wersäll 1958).

The characteristics of the acoustic reflex of the rabbit has earlier been investigated in acute animal experiments by Lorente de Nó & Harris (1933), Wersäll (1958) and Price (1963 *a*, *b*). The former used decorticated animals in which the responses of the muscles to pure tone stimulation were recorded by myographs. Wersäll (1958) used rabbits under light barbiturate anesthesia and recorded the muscle action potentials as well as the tension of the muscles. Price also used animals under light barbiturate anesthesia and recorded the change in the cochlear microphonic potential as a sign of activity of the middle ear muscles elicited by contralateral stimulation. In the early investigations by Lorente de Nó *et al* the stimulus strength was not given in terms of absolute sound pressure level as was done by Price and Wersäll. Price found that the curve for the threshold of the middle ear reflex as a function of frequency runs almost parallel to the ear's sensitivity curve determined as the sound pressure required to produce a standard cochlear microphonic potential. The difference between the sound level which produced a cochlear microphonic potential of 10  $\mu$ V and the threshold of the reflex was found to be 45–50 dB. In man the curve showing the sensitivity of the middle ear reflex at various frequencies, expressed as the intensity required to produce a given small impedance change, was also found to be almost parallel to the audibility curve for frequencies up to 4000 cps (Jepsen 1955; Møller 1962 *a*).

The results given by Price on the sensitivity of the rabbit's ear in terms of cochlear microphonic and on the sensitivity of the reflex were obtained in experiments on different ears. He recorded the change in the cochlear microphonic potential caused by middle ear muscle activity elicited by a sound in the opposite ear. The reflex threshold was defined as that sound intensity which was sufficient to produce a measurable change in the cochlear microphonic potential.

In man measurements of the changes in the ear's acoustic impedance are regarded as a convenient method for the study of the action of the middle ear muscles (Metz, 1946; Jepsen 1955; Møller 1958, 1961, 1962 *a*, *b*; Terkildsen & Nielsen 1960; Klockhoff 1961) and has also been applied in experiments on anesthetized cats (Gisselsson, Löfström & Metz, 1957; Møller 1964). Quantitative studies on *unanesthetized* animals, however, have not previously been performed.

The change in the ear's acoustic impedance to sound stimulation is a graded response which expresses the change in the acoustic properties of the middle ear caused by middle ear muscle activity and the measurements of changes in the acoustic impedance can be made on awake animals since they do not require any surgery.



FIG. 1 Impedance change in both ears in response to 200 cps pure tone of 200 msec duration applied to the left ear (left column) and to the right ear (right column). Solid lines represent impedance change in the left ear and the dashed lines show impedance change in the right ear. The scale in the upper right corner gives the impedance change as per cent of the maximal obtained change. The stimulus strength is 80 dB re 0.0002 b shown to the left.

The present paper deals with a study on the properties of the acoustic middle ear reflexes in unrestrained awake rabbits, the change in the acoustic impedance being used as a measure of the net activity of the two middle ear muscles. The change in acoustic impedance was measured on both ears simultaneously when the acoustic reflex was elicited by presenting sinusoidal sound stimuli to one ear at a time. In that way the crossed and the uncrossed reflexes were studied independently.

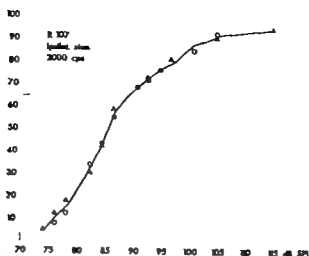


FIG. 2. Ipsilateral impedance change in per cent of maximal obtainable change as a function of stimulus intensity measured when the stimulus intensity was raised stepwise (triangles) and when it was raised stepwise (circles). The solid line shows the mean of 81 pairs of determinations.

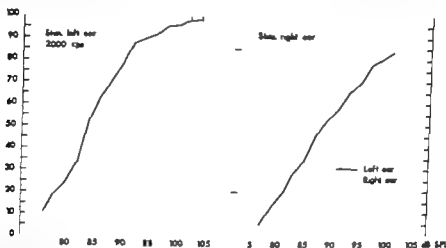


FIG. 3. Impedance change as a function of stimulus sound pressure level of 2000 cps pure tones with a duration of 200 msec. The reflex response in both ears is shown when either the left or the right ear was stimulated.

## METHODS

Seventeen rabbits weighing between 1.2 and 3.5 kg were used in a total of 81 experiments. No albino rabbits were used.

Rubber tubes were inserted in the ear canals and two identical impedance measuring devices were attached to these tubes. The tubes were secured in the ear canals by means of a dental molding material (Lastic 50) which within a few minutes provided a rubber like mold. Although the mold did not adhere to the walls of the ear canal it was held firmly in position because of the irregular shape of the ear canal and it could be removed easily at the end of the experiment.

The rabbits were sitting in a small box open at the top. They were not in any way tied and they usually sat quietly during the experiment which

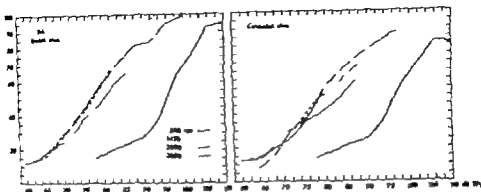


FIG. 4. Impedance change as a function of stimulus intensity  $I$  for different frequencies of 500 msec pure tones. The results are from one experiment.

could last several hours. In some of the experiments the position of the pinnae together with the impedance measuring devices was fixed by means of a piece of foam plastic in which carvings for the pinnae were made.

A sound source for eliciting the acoustic middle ear reflex was included in the impedance measuring device (Møller 1961). Pure tones, varied in steps of 2 or 4 dB were used (200 or 500 msec duration). The rise time of the tone to 90% of maximal amplitude was 2 msec and the time of decay to 10% of the maximum value was 2 msec. The sound stimulus was presented alternatively to the left and right ear while the intensity was increased stepwise from below the threshold of the reflex to the maximal intensity employed, and then lowered stepwise to values below the threshold. Thus the same intensity was presented twice to each ear.

The methods of recording the change in the ear's acoustic impedance were the same as that used in previous investigations on man (Møller 1961, 1962b). The acoustic impedance change was measured at a frequency of 800 cps. This sound was on continuously during the experiment and its sound pressure level was approximately 60 dB, re 0.0002  $\mu$ b, i.e. well below the reflex threshold. The impedance of the ear was balanced out electrically in the absence of stimulation and the change in the acoustic impedance appeared as a 800 cps signal, the amplitude of which was proportional to the magnitude of the changes in the ear's acoustic impedance. Recording were made from both ears simultaneously by means of two identical impedance measuring devices (see above). The responses were recorded on magnetic tape during the experiments and the data was processed at a later occasion.

The sound pressure level near the eardrum of the tone stimulus was measured when the apparatus was in place in the ear canal by using the earphone which during the impedance measurements supplied the 800 cps tone. A microphone (see Møller 1961). Such measurements were always performed at the end of each experiment and in many cases also at the beginning of the experiment.

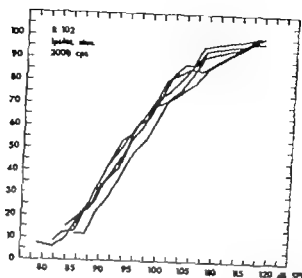


FIG. 5. Impedance change as a function of stimulus intensity measured in one rabbit at different occasions during one month. The stimulus was a 2000 cps pure tone and the ipsilateral response is shown.

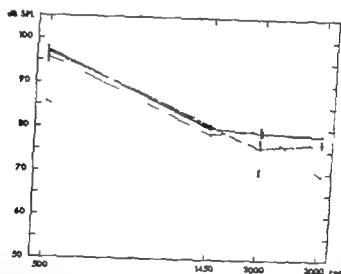


FIG. 6. The sensitivity of the ipsilateral reflex as a function of frequency obtained in 11 rabbits expressed as sound intensity required to produce 30% of the maximal obtainable impedance change. The connected symbols represent values obtained during the same experimental session in four different rabbits.

## RESULTS

Fig. 1 shows the acoustic impedance changes in both the left ear (solid line) and the right ear (dashed line) in response to a 2000 cps pure tone of 200 msec duration. The two columns of records show the responses elicited from the left and right ear respectively. The records of the impedance changes in the two ears were aligned with respect to amplitude in such a way that the maximal obtainable impedance change gave the same size of deflection in the two channels. This was accomplished in connec-





FIG. 7 Impedance change in both ears as a function of time elicited by one minute continuous pure tone with frequency of 2000 cps. The scales (the light of the impedance change in per cent of the maximal obtainable change).

tion with processing the data from the magnetic tape. As is seen the impedance change increases with increasing stimulus strength and the impedance change for a certain stimulus intensity is larger in the ipsilateral than in the contralateral ear. The shape of the curves having equal amplitude is similar both for ipsilateral and contralateral stimulation.

The magnitude of the impedance change measured immediately before the termination of the stimulus and expressed in per cent of maximal obtainable ipsilateral response was plotted as a function of the stimulus intensity (Fig. 2). The triangles in Fig. 2 represent the amplitudes of the responses obtained when the stimulus intensity was raised stepwise, and the circles represent the values obtained when the stimulus was lowered stepwise. The lack of hysteresis shows that the results were not affected by fatigue or facilitation. The mean of such pairs of values fall along a curve (solid line) which shows the impedance change as a function of stimulus intensity (given in dB relative 0.0002  $\mu$ b (SPL)).

Fig. 3 shows the amplitude of the reflex response in both ears as a function of stimulus intensity when the left or the right ear were stimulated. The diagram shows that within the whole intensity range investigated the ipsilateral reflex requires a lower sound intensity than the contralateral for the same response. The mean of this difference measured at 20% of maximal impedance change obtained in a total number of 68 experiments, is 2 dB ranging from -3 dB to +7 dB.

Fig. 4 shows the impedance changes as a function of stimulus intensity for pure tones of four different frequencies. There is no significant difference in the slope of the curves. One would expect that the curve for the higher stimulus frequencies should be steeper than that for the lower fre-



FIG. 8. Impedance change in the ipsilateral (upper row of points) and contralateral ear (lower row) to repetitive stimulation with 2000 cps tone burst of 20 msec duration at a rate of 1 per second.

quency (500 cps) since a contraction of the middle ear muscles provides a greater decrease in sound transmission at low than at high frequencies and thus extends the intensity range of the middle ear reflex at low frequencies. This unexpected result illustrated in Fig. 4 will be dealt with in the discussion.

In order to determine the day-to-day variation of the reflex function, 4 rabbits were tested with intervals of one day to several months. The variations were found to be independent of the length of the interval and the range was 3 dB. Fig. 5 shows a typical family of five stimulus response curves of the ipsilateral reflex obtained in one animal at different occasions during one month. As seen there are shifts within a range of 3 dB without any change in slope. The response varies more near threshold than at response values above 20% and the variation of 3 dB refers to the responses between 20% and 70% impedance change. Thus, the reproducibility is good and the accuracy of the measurements is in the order of magnitude with which the sound pressure level of the stimulus can be controlled.

Fig. 6 shows the sensitivity of the ipsilateral reflex as a function of frequency obtained in 11 rabbits. The connected symbols represent values obtained during the same experimental session. The sensitivity is expressed as the stimulus intensity required to produce 20% of the maximal obtainable impedance change. As seen the threshold expressed in this way (cf. Möller 1961) is nearly constant between 1450 and 3000 cps while at 500 cps it is about 15 dB higher.

#### *Response to Long Duration Stimulation*

Fig. 7 shows the impedance change in response to continuous stimulation with a tone with a frequency of 2000 cps and a duration of 60 sec. The stimulus intensity was 63 dB SPL or approximately 20 dB above the reflex

threshold. Both the ipsilateral and contralateral stimulation are followed by a sustained response which does not show any significant change during stimulation. It should also be noted that after termination of the stimulus the relaxation of the muscles is much slower than after stimulation of short duration (cf Fig. 1). Finally the amplitude of the responses to repetitive stimulation with tone bursts of 200 msec duration (frequency 2000 cps) presented at a rate of 1 per second is plotted versus time in Fig. 8. As seen, there is only a slight diminution of the amplitude of the impedance, the reduction, after 140 seconds of stimulation, being only 10% of maximal obtainable impedance change. This value corresponds to a decrease in the sensitivity of about 3 dB both on the ipsilateral and contralateral side.

### DISCUSSION

The present investigation shows that the acoustic middle ear reflex can be investigated on awake, unrestrained rabbits with the aid of the technique which has been used in humans without any surgery. The functional characteristics of the acoustic middle ear reflex in rabbits, covered by the present study shows great similarities in general with those of the human middle ear reflex studied with the same technique. As in humans, the ipsilateral reflex has a higher sensitivity than the contralateral, the mean difference being about 2 dB in rabbit (Fig. 3) compared with 2-14 dB in man (Møller 1961). The sensitivity of the ipsilateral reflex measured as the intensity required to produce 20% of the maximal obtainable impedance change was found to be 70-80 dB SPL for frequencies between 1450 and 3000 cps and 85-100 dB for 500 cps (see Fig. 6). These values are roughly 10 dB lower than the corresponding values for humans at 1450-3000 cps and almost identical to 500 cps.

Price (1963) measured the sensitivity of the contralateral middle ear reflex in the rabbit by recording the change in the cochlear microphonics. Since his experiments were performed on lightly anesthetized preparations, the slightly higher threshold values that he obtained for the contralateral reflex seem to be due to the effect of the anesthetic drug.

According to studies on the cat with other methods for recording the muscle activity the magnitude of the reflex response is highly variable. The reflex excitability has thus been reported to depend on such factors as the animals' attention, state of wakefulness, etc. In the present study the response measured on different occasions showed very little variations and its reproducibility corresponded to the accuracy with which the sound pressure of the stimulus could be reproduced from time to time. The high degree of reproducibility does not directly rule out the possibility that the reflex response may vary due to variations in the attention and alertness. However it seems unlikely that it should be possible to perform a great number of experiments over a long period of time with the animal in the same state of alertness and attention.

Wersäll (1958) who measured the tension of the tympanic muscles in animals under light anesthesia and on decorticate animals showed a considerable fatigue when sounds of high intensity were used. He further reported that weaker sounds did not produce any appreciable fatigue which is in accordance with the results of the present investigation.

It is known that the contraction of the middle ear muscles decreases the transmission of low frequencies through the middle ear and thus reduces the volume displacement at the oval window. Therefore one would expect that the slope of the stimulus response curve at a low frequency should be less than at higher frequencies as is actually the case in man. As mentioned above no such difference in the slope was found in the present investigations on rabbits (see Fig. 4). This somewhat unexpected result may be explained by the fact that the frequency range within which a contraction of the tympanic muscles reduces the middle ear transmission can be expected to be greater in the rabbit than in man (Möller 1965). It is therefore possible that in rabbit the effect of reflex on the middle ear transmission is almost the same within the entire frequency range investigated. It is also possible that the relationship between the magnitude of the volume displacement of the cochlear fluid and the reflex contraction varies as a function of frequency.

#### ACKNOWLEDGMENTS

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#### ZUSAMMENFASSUNG

Es wird gezeigt, dass in der gleichen Weise wie es in früheren Arbeiten schon für das menschliche Ohr beschrieben worden ist, das Verhalten des akustischen Mittelohrreflexes auch beim Kaninchen durch Messung der Änderung der akustischen Impedanz untersucht werden kann. Das Kaninchen ist dabei vollkommen wach und in seiner Bewegung nicht beschränkt. Die Empfindlichkeit des Reflexes wurde im Bereich zwischen 500 und 3000 Hz gemessen. Die Reproduzierbarkeit bei Messungen an dem gleichen Kaninchen lag in der Grösse von 3 dB über den Zeitraum eines Monats, dagegen zeigte sich eine beträchtliche interindividuelle Variation. Die Messungen ergaben ferner, dass die Empfindlichkeit des Reflexes etwas höher bei ipsilateraler Aktivierung war als bei kontralateraler Stimulation. Des weiteren konnte auch festgestellt werden, dass der Reflex bei Beschallung von 1 min Dauer mit einem 1000-Hz Ton kein merkliches Abklingen zeigt.

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## THE SPIRAL GANGLION IN PROFOUND DEAFNESS

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The spiral ganglion cell population was evaluated in 41 ears from 29 profoundly deaf patients. In 10 ears 66 to 100 per cent of the spiral ganglion cells remained. In 3 ears 33 to 66 per cent of the cells remained and in 28 ears less than 33 per cent remained. In all of these ears there was severe atrophy of the organ of Corti. When the etiology of the deafness is known it often is possible to predict the condition of the ganglion. An excellent ganglion cell population would be expected if the deafness was due to ototoxic drugs and a severe loss of ganglion if due to bacterial labyrinthitis.

Profound deafness means the absence of detectable hearing by routine testing methods. For practical purposes it can be regarded as total sensory deprivation be it auditory, visual or some other modality has a remarkable effect on the reactions of the entire individual. Profound deafness is a particularly depressing psychological condition largely related to the feeling of social isolation. Despite lip reading, instruction and general supportive measures these individuals tend to become secluded, lonely and often disgruntled. Anything that might help them to re-establish sonic contact with the outside world would be of value. The ability to hear and discriminate normal speech is the most desirable objective but even indistinct speech would help to facilitate lip reading. The ability to hear such sounds as the closing of doors might relieve the feeling of isolation.

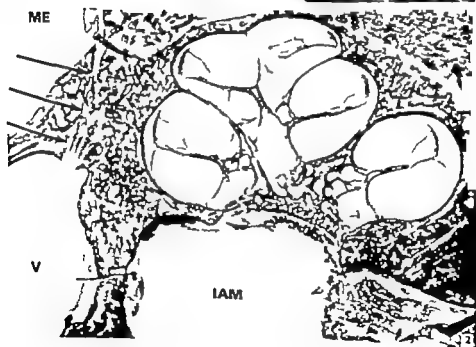
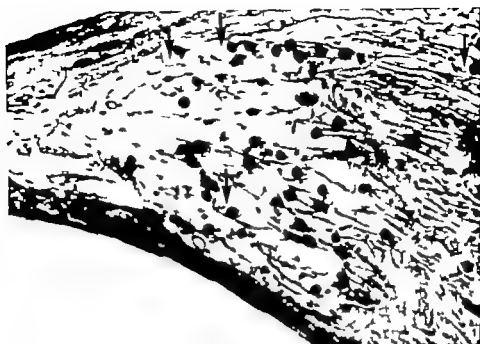
Direct stimulation of the cochlear nerve has been considered for many years as a possible means of providing hearing for some of these individuals and some reports of such attempts have been published (Djourno *et al* 1957, Doyle *et al* 1964, Simmons, 1966). In all of these the ability to hear some sounds has been accomplished although such complex activities as

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Fig. 1. The spiral ganglion of cat with intracranial concussion without skull fracture resulting from a head blow (Schuknecht *et al* 1931). Behavioural test performed 3 months after the injury showed the animal to be totally deaf. Histologic studies showed almost complete disappearance of the organ of Corti but few spiral ganglion cells remain. Each neurone has a normal appearing central soma but the peripheral fiber is



missing and large clear acoust is located at the peripheral pole of the neurone  
or case

Fig. 2 Transverse fracture of the temporal bone, patient (D.D.) Death occurred 4 months  
after this fracture as the result of another accident. The fracture line, indicated by  
arrows, extends from the middle ear (ME) through the vestibule (V) IAM (internal  
auditory meatus).

speech discrimination were not achieved. Recent studies on stimulus coding in single fibres of the auditory nerve suggests the possibility of development of prosthetic devices that could convert sound energy into patterns of electrical impulses similar to those found in that nerve (Kiang, 1965). A problem will remain in getting this coded pattern of electrical impulses into the appropriate functioning fibers of the eighth nerve. Our concern in this publication is not in the technical aspects of stimulation of the nerve but in the availability of nerve fibers to be stimulated.

For any method of direct excitation of the eighth cranial nerve to succeed in transmitting complex signals, there must be an adequate population of functioning cochlear nerve fibers. Therefore an attempt was made to determine the ganglion cell population (and thus the auditory fibers) in ears showing profound deafness from various etiologies. This would establish the feasibility of direct stimulation in these cases.

The assumption that the spiral ganglion population reflects the numbers of auditory nerve fibers is supported by histological studies in animals and humans. It is a known fact that when the central fibers of the spiral ganglion cells are injured the cell bodies of the involved neurones will degenerate in 2 to 3 weeks. Similarly when the peripheral fibers are injured, the cell bodies of the injured cells usually disappear. It has been noted that a few may remain possibly as many as 10% in certain disease conditions. In these ears the cell body is shrunken with a pyknotic nucleus. There is an intact central axone and a vacuole at the pole representing the location of the missing peripheral axone (Fig. 1). We believe that in the determination of functional neural units the error introduced by counting cell bodies rather than peripheral nerve fibers is not greater than 10%.

## PROCEDURE AND RESULTS

The temporal bone collection of the Massachusetts Eye and Ear Infirmary contains over 500 sets of specimens with documented histories. This study has included only those ears where direct stimulation of the cochlear nerve would have been a practical possibility. Thus those cases were excluded where the deafness was due to acoustic neuroma or where life expectancy was limited because of severe congenital abnormalities or secondary malignant lesions in the temporal bone. In the collection there are some cases where total deafness was present for less than 3 months before death, and these also have been excluded because the time lapse may have been insufficient for degenerative changes to have been completed. The total number of suitable ears in the Massachusetts Eye and Ear Infirmary collection is 34 and to these are added 7 ears from the University of Chicago's collection to give a total of 41 ears from 20 patients.

The serially sectioned temporal bones were examined and the spiral ganglion cell population estimated for several regions of the cochlea



TABLE 1  
Ganglion cells supplying the 11 to 24 mm region of the cochlea

Etiology	Ganglion cells present			Total
	A. 2/3 to normal	B. 1/3 to 2/3	C. Less than 1/3	
Congenital	3	—	2	4
Transverse fracture	1	—	—	1
Bacterial labyrinthitis	—	1	16	17
Viral labyrinthitis	3	1	5	9
Congenital syphilis	—	—	2	2
Vascular	—	1	1	2
Kanamycin intoxication	2	—	—	2
Otosclerosis	2	—	2	4
Total	10	3	28	41

The 11 to 24 mm regions of the cochleas are determined from graphic reconstructions according to the well established methods described by Guild (1921) and Schuknecht (1953). This region of the cochlea is most important for speech reception based on current knowledge of the spatial distribution of frequency response in the human cochlea.

(1) the region from about 11 mm to 24 mm along the organ of Corti, corresponding to that part of the cochlea most important for speech reception (500 cps to 4000 cps) (2) the basal turn, basal end to about 18 mm (3) the middle turn, about 18 mm to 28 mm, and (4) the apical turn from about 28 mm to the apical end, which is located at about 32 mm.

The assessment of the numbers of spiral ganglion cells is based on experience developed in the study of several hundred ears by the authors and the final estimates were determined by mutual agreement. Although the counting of ganglion cells would increase the accuracy, this degree of precision was not required for this study.

It seems likely that the various neural units may have been assigned different functions, for it has been established that the peripheral axones have several different types of distribution e.g. some end mainly on inner hair cells and others mainly on outer hair cells (Fernández, 1951). Therefore if the degenerative process should involve the selective loss of a functional type of neurone, the psycho-acoustic manifestations would reflect this selectivity. For these reasons we believe that attempts to closely correlate ganglion cell loss with functional deprivation is of limited value.

To minimize the dangers of incorrect assessment, the estimates have been limited to expressions in thirds of normal, i.e. (a) more than 2/3 of the normal number present, (b) between 1/3 and 2/3 present and (c) less than 1/3 remaining. The findings are summarized in Table 1 following which is a more detailed description of the pathological changes in the various disease conditions for which specimens were available.

TABLE 2 *Congenital*

	11 to 24 mm	Cochlea turn		
		Basal	Middle	Apical
K. F. Schelbe 1	A	A	A	A
C. V. Schelbe 2	A	A	A	A
C. G. Schelbe 3	C	C	C	C
P. M. Mondini	—	B	—	—

It is not possible to determine the speech frequency area of the cochlea of this ear.

### *Congenital deafness*

A detailed discussion of the pathological findings in profound congenital deafness is beyond the scope of this present communication which is limited to those ears in our collection from patients who had a normal life expectancy at birth. The data is shown in Table 2 and includes 3 ears with cochleo-saccular aplasia (Scheibe) of genetic etiology and one with Mondini type aplasia (single cochlear coil) from 4 patients.

It is encouraging to note that 2 of the 3 ears with the Scheibe defect have at least 2/3 of the normal number of spiral ganglion cells, and the ear with Mondini type aplasia has a good population in the only existing turn of the cochlea.

### *Transverse fracture of the temporal bone*

The transverse fracture of the temporal bone occurs perpendicular to the long axis of the petrous pyramid and traverses the vestibule of the inner ear resulting in degenerative changes in the sensory structures, usually with complete loss of cochlear function (Grove 1939; Proctor *et al.* 1956). One such ear in our series has a good population of nerve fibers (Fig. 2 and Table 3).

### *Bacterial labyrinthitis*

Bacterial labyrinthitis is a common cause of bilateral profound deafness, usually occurring secondary to either otitis media or meningitis. In the 17 ears studied there is severe destruction of the membranous labyrinth usually with severe loss of the spiral ganglion (Fig. 3 and Table 4). In most of these ears there would be no possibility of achieving any useful hearing by direct stimulation of the cochlear nerve.

TABLE 3 *Fracture*

	11 to 24 mm	Cochlea turn		
		Basal	Middle	Apical
D. D.	A	A	A	A

TABLE 4 Bacterial labyrinthitis

		Cochlear turn			
		11 to 24 mm	Basal	Middle	Apical
F. U.	R	C	C	C	C
	L	C	C	C	C
E. D.	L	C	C	B	B
F. F.	L	C	C	C	C
G. H.	R	C	C	C	C
	L	C	C	C	C
M. O.	R	■	C	V	A
Z. S.	R	C	C	C	C
L. Z.	R	C	C	C	C
	L	C	C	C	C
E. McV.	R	C	C	B	A
	L	C	C	B	A
M. McK.	R	C	C	B	A
C. G.	R	C	C	C	C
	L	C	C	C	C
C. K.	R	C	C	C	C
	L	C	C	C	C

*Viral labyrinthitis*

The hearing loss in viral infections of the labyrinth range in severity from mild to total and of the latter 9 ears from 6 patients are available for study.

The common factor in all cases is degeneration of the organ of Corti which is more marked in the basal turn. The extent of degeneration of the spiral ganglion usually parallels the degree of damage to the supporting cell of the organ of Corti. There is an obvious exception to this in the mumps labyrinthitis case (Lindsay *et al.* 1960) in which there is total absence of the organ of Corti in the basal turn on both sides with the presence of an almost normal number of cochlear neurones.

Viral labyrinthitis apparently can produce all degrees of inner ear change from mild lesions of the basal turn to severe diffuse destruction of the organ of Corti. Thus the amount of spiral ganglion available in these ears cannot be predicted accurately and this is obvious from the data in Table 5. Whenever proof of the viral aetiology for the case of sudden deafness is lacking, the pathological changes are similar to those occurring in known mumps and measles labyrinthitis.

*Syphilitic labyrinthitis*

Some patients with congenital syphilis develop a profound bilateral hearing loss and histological studies of ears from such individuals show degenerative changes in the organ of Corti (Harmon & Schuknecht, 1966). In this series there are 2 ears from 2 patients with congenital syphilis, both

TABLE 2 *Congenital*

	Cochlea turn			
	11 to 24 mm	Basal	Middle	Apical
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C. V. Scheibe 2	A	A	A	A
C. G. Scheibe 3	C	C	C	C
P. M. Mondini	—	II	—	—

It is not possible to determine the speech frequency area of the cochlea of this case.

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A detailed discussion of the pathological findings in profound congenital deafness is beyond the scope of this present communication which is limited to those ears in our collection from patients who had a normal life expectancy at birth. The data is shown in Table 2 and includes 3 ears with cochleo-saccular aplasia (Scheibe) of genetic etiology and one with Mondini type aplasia (single cochlear coil) from 4 patients.

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### *Bacterial labyrinthitis*

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TABLE 3 *Fracture*

	Cochlea turn			
	11 to 24 mm	Basal	Middle	Apical
D. D.	A	A	A	A

TABLE 4 Bacterial labyrinthitis

			Cochlea turn		
			Basal	Middle	Apical
F.B.	R	C	C	C	C
	L	C	C	C	C
E.D.	L	C	C	B	B
P.F.	L	C	C	C	C
G.H.	R	C	C	C	C
	L	C	C	C	C
M.O.	R	B	C	\	\
Z.A.	B	C	C	C	C
L.Z.	R	C	C	C	C
	L	C	C	C	C
B.M.M.	R	C	C	B	\
	L	C	C	B	\
M.M.H.	R	C	C	B	\
C.G.	R	C	C	C	C
	L	C	C	C	C
C.H.	R	C	C	C	C
	L	C	C	C	C

*Viral labyrinthitis*

The hearing loss in viral infections of the labyrinth range in severity from mild to total, and of the latter 9 ears from 6 patients are available for study.

The common factor in all cases is degeneration of the organ of Corti which is more marked in the basal turn. The extent of degeneration of the spiral ganglion usually parallels the degree of damage to the supporting cell of the organ of Corti. There is an obvious exception to this in the mumps labyrinthitis case (Lindsay *et al* 1960) in which there is total absence of the organ of Corti in the basal turn on both sides with the presence of an almost normal number of cochlear neurons.

Viral labyrinthitis apparently can produce all degrees of inner ear change from mild lesion of the basal turn to severe diffuse destruction of the organ of Corti. Thus the amount of spiral ganglion available in these ears cannot be predicted accurately and this is obvious from the data in Table 5. Whereas proof of the viral etiology for the case of sudden deafness is lacking, the pathological changes are similar to those occurring in known mumps and measles labyrinthitis.

*Syphilitic labyrinthitis*

Some patients with congenital syphilis develop a profound bilateral hearing loss and histological studies of ears from such individuals show degenerative changes in the organ of Corti (Karmody & Schuknecht, 1966). In this series there are 2 ears from 2 patients with congenital syphilis, both

TABLE 5 *Viral labyrinthitis*

		Cochlea turn			
		11 to 24 mm	Basal	Middle	Apical
N. A.	R Measles	C	C	C	C
	L	C	C	C	C
R. O.	R Measles	C	C	C	C
	I	C	C	C	C
R. P.	I	C	C	C	C
P. C. <sup>b</sup>	I Sudden deafness	B	B	B	A
A. M. <sup>c</sup>	R Rhino-pharyngitis	A	A	A	A
A. W. <sup>d</sup>	R Mumps	A	A	A	A
	L	A	A	A	A

<sup>a</sup> H cck (1961)

<sup>b</sup> Schuknecht *et al* (1962)

Beal *et al* (1967)

<sup>d</sup> Lindsay *et al* (1960)

exhibiting marked damage to the organ of Corti and corresponding degeneration in the spiral ganglion (Table 6)

While acquired syphilis only rarely affects the labyrinth similar degeneration takes place (Goodhill 1930) and therefore it can be anticipated that patients totally deaf from syphilis will have a degenerated spiral ganglion and are unlikely to benefit from attempts at direct stimulation of the cochlear nerve.

#### *Kanamycin intoxication*

The ototoxic effect of certain antibiotics have been known for over 20 years (Brown & Hinshaw 1946) and streptomycin was used as early as 1948 for the destruction of the vestibular endorgans in the treatment of Menière's disease (Fowler 1948). With the passage of time there was an increasing number of clinical (Glorig, 1951) and experimental (Berg, 1949)

TABLE 6 *Syphilis*

		Cochlea turn			
		11 to 24 mm	Basal	Middle	Apical
L. F.	L	C	C	B	B
E. M.	L	C	C	C	C

FIG. 3 Bacterial labyrinthitis has resulted in complete loss of the organ of Corti and near total loss of spiral ganglion cell (patient C.K.). The scalae contain fibrous tissue and bone (B). I.I.M. Internal auditory meatus.

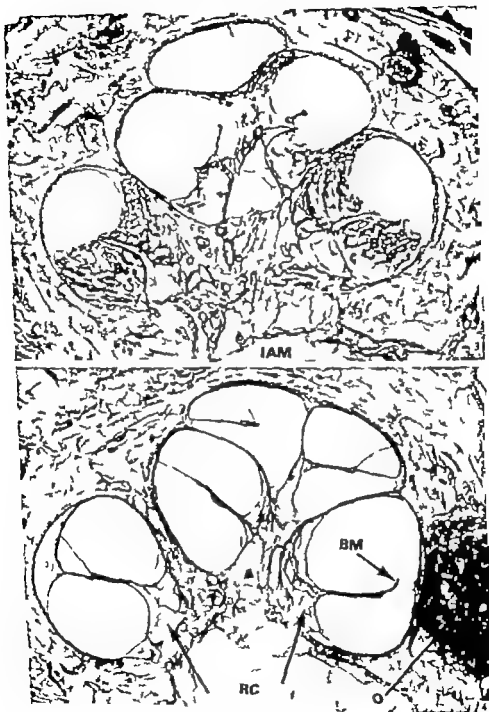


FIG. 4 Otosclerosis associated with profound deafness (patient A.B.). The basilar membrane (BM) is ruptured in the region of spiral ligament atrophy adjacent to the otosclerotic focus (O). Only a few spiral ganglion cells are seen in Rosenblatt canal (RC).

TABLE 7 *Ototoxic drugs*

	Cochlea turn			
	11 to 24 mm	Basal	Middle	Apical
L. C. R	A	A	A	A
L	A	A	A	A

reports of damage to the labyrinthine structures following the administration of antibiotics, but it was not until 1960 that histological findings were reported in the human (Lindsay *et al* 1960). This case demonstrated severe hair cell damage following the administration of neomycin with lesser degrees of degeneration of the supporting structures and good preservation of the spiral ganglion.

Since then further histological reports have appeared on the effect of several "mycin" drugs on humans (Benitez *et al* 1962) and animals (McGee & Olszewski 1962, Ward & Fernández, 1961, Farkashidy *et al.*, 1963). Although there is some variation the overall consensus of opinion is that the hair cells of the organ of Corti especially the outer hair cells, are the most susceptible to the ototoxic effect of these drugs. The supporting cells are involved occasionally especially after high dosage of the drugs. It is also apparent that the ganglion cells survive when the supporting cells are not damaged.

Table 7 shows the findings in the spiral ganglion in patient L. C. who was given 12 grams of kanamycin during an 8 day period for the treatment of pycelonephritis. She died 3 months later of kidney failure (Igarashi & Yoshinobu 1963).

The histological findings in intoxication with guanine (Rüedi *et al* 1952) and nitrogen mustard (Cummings) show a similar tendency to destruction of the hair cells with little or no damage to supporting cells and good ganglion cell population if their corresponding supporting cells have escaped damage.

It is to be expected therefore that in most patients with deafness due to the administration of ototoxic drugs, a good population of spiral ganglion cells will be present.

### *Vascular occlusion*

In this series there are 2 ears from a patient who experienced 2 episodes of sudden complete and permanent hearing loss. The first at the age of 52 in the left ear and the second at 65 in the right ear. She suffered 2 cerebro-vascular accidents after the age of 60 years and died of bronchopneumonia at 85 years of age.

From the history and histological findings, the etiology is presumed to have been vascular occlusion. In the left ear the damage to the organ of



TABLE 8. Vascular

	11 to 24 mm	Cochlea turn		
		Basal	Middle	Apical
B. W. H.	B	B	H	A
L.	C	C	E	B

Corti is reflected in the spiral ganglion in which there are a few ganglion cells at the basal end where the sensory endorgan is completely missing. There is a moderate population at the apex where the damage is less severe. The findings are shown in Table 8.

Even when histological studies are available it is not possible to state with certainty the cause of sudden deafness in all cases. The decision as to the etiology must be based on associated findings such as peripheral vascular occlusion, strokes, or myocardial infarction.

#### Otosclerosis

Sensorineural deafness in association with otosclerosis is a common finding but there is much controversy as to whether there is an etiological relationship or whether the perceptive loss is simply coincidental. This point has been discussed at great length elsewhere (Schuknecht, 1966; Schuknecht & Cross, 1966; Lindsay & Beal, 1966; Wolff, 1966; Altmann, 1966; Nager, 1966; Linthicum, 1966; Rüdel & Spöndlin, 1966) and will not be dealt with here except to consider those cases in which there is profound hearing loss in association with otosclerosis. While it appears unlikely that otosclerosis frequently affects the function of the inner ear there is no doubt that it can do so.

In this series there are 4 ears from 3 patients with profound deafness presumably due to otosclerosis and the findings are shown in Table 9.

In the right ear of patient A B there is severe atrophy of the organ of Corti and spiral ganglion and rupture of the basilar membrane presumably due to extreme atrophy of the spiral ligament (Fig. 4). The other 2 ears in this group show moderate degeneration of the organ of Corti

TABLE 9. Otosclerosis

	11 to 24 mm	Cochlea turn		
		Basal	Middle	Apical
A. B. H.	C	C	C	E
L.	C	C	C	E
F. A. H.	A	A	A	A
V. R. A.	A	A	A	A

but the most striking finding is atrophy of the spiral ligament with rupture of the basilar membrane accompanied by good preservation of the spiral ganglion

On this evidence of 4 ears, the spiral ganglion may be severely degenerated or well preserved but there are no clinical means of predicting the situation

### CONCLUSIONS

The plight of the totally deaf is such that any sonic contact with the outside world may help. Some attempts at direct stimulation of the eighth cranial nerve have been reported and while many problems remain, there is hope that this procedure can be developed to be of some value for these unfortunate individuals.

If any method of direct stimulation is to succeed in transmitting complex signals such as speech an adequate population of functioning auditory nerve fibers will be necessary. Experimental studies have shown that pure tone thresholds may be normal when no more than 25% of the spiral ganglion cells remain in the region of the cochlea serving the frequencies being tested (Schuknecht & Woellner 1953). The number of ganglion cells required for socially adequate hearing for speech has not been determined however studies in progress in our laboratory by Otte suggest that a ganglion cell population in the speech frequency area of the cochlea which is 2/3 or more of normal can provide useful speech reception.

We have evaluated the ganglion cell population and thus the auditory fibers of the eighth nerve, in ears having profound sensorineural deafness of various etiologies to establish the possibilities of direct stimulation in these patients.

The patterns of degenerative change in the spiral ganglion were consistent for some etiologies and inconsistent for others. It appears that the spiral ganglion population can be expected to be good in ears profoundly deaf from some genetic types of congenital deafness, temporal bone fractures, and ototoxic drugs. A poor population of ganglion cells would be expected in profound deafness due to bacterial labyrinthitis and congenital syphilis. When profound deafness is due to viral labyrinthitis, vascular occlusion or otosclerosis, the extent of degeneration of the ganglion is variable and there is no clinical means of assessing the population of the remaining ganglion cells.

In our series of 41 ears from 20 profoundly deaf patients, there were 10 ears with more than 2/3 of the spiral ganglion cells remaining, 3 with 1/3 to 2/3 remaining and 28 with less than 1/3 remaining. If we assume that 2/3 or more of the spiral ganglion cells are needed for useful speech reception given a physical means of reproducing cochlear function, then 10 of 41 ears, or 24% meet the selection criterion. When the etiology of the deafness is known however the ability to predict the condition of the ganglion is greatly improved. An excellent population of ganglion cells

would be expected if the deafness was due to ototoxic drugs and a severe loss if due to bacterial labyrinthitis.

Fewer ganglion cells are required for the identification or differentiation of simple acoustic stimuli such as the telephone bell, slamming doors, or thunder than for speech and probably even fewer are needed for the detection of noise.

Of that total of 41 ears we have found 13 to have less than 10% of the ganglion cells remaining, and of these, 9 have less than 1% remaining. Although it is presently not possible to predict the potential for electrical stimulation in ears with ganglion cell losses of these magnitudes, it is certain that the complexity of stimuli which can be impressed upon the acoustic nerve and transmitted to the brain depends upon the number of available functional neural units.

### ZUSAMMENFASSUNG

Die Spiralganglionzellbevölkerung wurde in 41 Ohren von 29 hochgradig schwerhörigen Patienten eingeschätzt. In 10 Ohren blieben nur 66 bis 100 Prozent in 3 Ohren in 33 Prozent und in 28 Ohren weniger als 33 Prozent der Spiralganglionzellen erhalten. In all diesen Ohren wurde eine schwere Atrophie des Corti sehen Organs festgestellt. Wenn die Ätiologie der Schwerhörigkeit bekannt ist, ist es oft möglich auch den Zustand der Spiralganglien vorauszusagen. Eine ausgezeichnete Ganglionzellbevölkerung kann man erwarten, wenn die Schwerhörigkeit durch toxische Medikamente bedingt ist und ein schwerer Verlust an den Ganglionzellen durch bakterielle Labyrinthitis verursacht ist.

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## THE EFFECT OF WATER IMMERSION ON PERCEPTION OF THE OCULOGRAVIC ILLUSION IN NORMAL AND LABYRINTHINE DEFECTIVE SUBJECTS<sup>1</sup>

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The separate and combined influences of otolith and nonotolith sensory inputs upon perception of the oculogravic illusion were investigated by manipulating the *visual and gravito-inertial force environment*. By comparing the visually perceived direction of space by four naval aviators and four deaf persons with bilateral labyrinthine defects when dry and when immersed in water up to neck level, the contributions of (1) fluid force receptors in the vestibular organs and (2) non-vestibular proprioceptors stimulated by external contact support could be differentiated. Under these various conditions it was found that in normal persons, the vestibular contribution is predictable in terms of the direction of the gravito-inertial force vector but that the non-vestibular contribution varies (it may be relatively great or small). In persons with bilateral labyrinthine defects a no vestibular contribution was always present but there was great individual variance. The significance of the findings in terms of tests measuring the function of the otolith organs is discussed.

This report describes an experiment in which sensory inputs influencing the visually perceived direction of space were measured. A person is poised to perceive these influences if, for example, he is subjected to centripetal force while in a fixed position on a human centrifuge. The change in direction of the gravito-inertial vertical with reference to his body is rightly interpreted as a tilt away from the upright, and the visual framework tends to tilt concordantly. The latter phenomenon is a form of apparent motion which for convenience has been termed the oculogravic illusion (Graybiel, 1952).

This illusion, first described by Purkinje (1820) was the object of investigation by Mach (1873) who reasoned that it must have its genesis in a sensory organ in the skull, and the nonacoustic labyrinth was implicated. Barani (1952) regarded the illusion as having its origin in the vestibule.

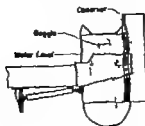
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Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the view or endorsement of the Navy Department.

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CEMAT CENTRIFUGE

FIG. 1. Gondola for human centrifuge under wet and dry conditions.

their significant clinical findings are summarized in Table 1. All had suffered from meningitis in childhood, one at pre-school age. Their otolith function was determined by means of ocular counterrolling. The counterrolling index (CI) is defined as one-half the sum of the maximum rightward and leftward ocular counterroll when the subject is tilted 25° 30° and 45° from the upright. Typical values for normal and L-D subjects do not overlap (Viller II & Graybiel 1963). The L-D subjects were thoroughly familiar with all aspects of the experiment except those dealing with centrifugation under water.

The aviators, 26 to 32 years of age, were in excellent health and performance had met the stringent medical requirements for duty involving flying. None had a history of middle ear disease. Routine hearing and caloric tests revealed no significant abnormality. Their counterrolling indices, obtained at 50-degree maximal tilt, ranged from 241 to 434. All were experienced in taking tests of many kinds, but none was familiar with the procedures in this experiment.

#### Apparatus

The heavy duty centrifuge at General Dynamics Astronautics (San Diego, Calif.) was modified for our purpose. It was hydraulically driven, with adequate performance characteristics and excellent rotary coaxial connections. A gondola was fabricated that consisted of a cylindrical tank and observer's platform mounted in a trunnion 18.08 feet from the center of rotation (Fig. 1). It was equipped with a suitable water heater, closed circuit television, and voice communication system. By means of a pneumatic piston the whole assembly could be rotated about the trunnion pins through an arc of 45° in a period of 30 seconds with the centrifuge stationary or rotating. Inside the tank a metal seat was fitted to a rail system and could be removed, along with the subject, by means of a hoist. Bolted to the seat was the rear half of a fiberglass body mold prepared for each subject; the front half was secured by "quick release" metal locks.

A visual test goggles (VTG) was devised which represented a modification of a visual target device used previously (Clark & Graybiel, 1952). On the

(otolith apparatus) when 13 of 32 "deaf mutes" failed to perceive it. Our early experimental findings (Graybiel 1956) using deaf persons with bilateral labyrinthine defects (L-D subjects) seemed to confirm Kreidl's work with minor qualifications. Later in a systematic study the settings of 10 L-D subjects were compared with those of nine normal subjects under identical conditions (Graybiel & Clark 1965). The normal subjects readily perceived the apparent rotation of the target (oculogravic illusion) and their estimates bore a meaningful relation to the angular changes in the gravito-inertial horizontal. Individual variance in these subjects was manifested chiefly in their overestimation of the illusion when they were exposed to relatively large changes in direction of the force vector. None of the L-D subjects made settings comparable to those of the normal subjects. The only consistent L-D performers were four who perceived little or no illusion; the others expressed varying degrees of difficulty in making the settings which were characterized by inter- and intra-individual variance.

Although the inferior performance of the L-D subjects was ascribed to loss of otolith function, there was no correlation between the magnitude of the settings and the degree of ocular counterrolling, a measure of otolith function (Woellner & Graybiel 1959; Müller II 1962). It was hypothesized that the differences among the L-D subjects in perceiving the oculogravic illusion might be explained by residual otolith function, by inputs from nonotolith proprioceptors or by a combination of both.

The present experiment was designed to test this hypothesis by exposing normal and L-D subjects to centrifugation under dry condition and when immersed in water. Field force receptors in the otolith organs would not be affected by the immersion while nonotolith proprioceptors, mechanoreceptor systems, would be minimally stimulated.

Two classes of phenomena relating to visual space perception can be studied while systematically manipulating the force environment. One class deals with "interactions" in which cues to a visual frame of reference are available, the other with "influences" in which visual cues are either lacking or inadequate. In the present experiment we took advantage of the extraordinary circumstance in which a dim line of light in darkness is an inadequate cue yet can be manipulated to indicate the visually perceived direction of space. In using such a visual target "influences" are being studied. Their threshold of effect, i.e. the threshold for perception of the oculogravic illusion under ideal conditions, is a change in direction of the gravito-inertial horizontal of approximately 15° (Graybiel & Patterson Jr 1955).

## PROCEDURE

### *Subjects*

Four naval aviators and four deaf persons with bilateral labyrinthine defects participated. The four L-D subjects were in good general health.



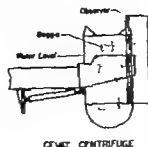


FIG. 1 Gondola for human centrifugation under wet and dry conditions.

their significant clinical findings are summarized in Table 1. All had suffered from meningitis in childhood, one at pre-school age. Their otolith function was determined by means of ocular counterrolling. The counterrolling index (CI) is defined as one half the sum of the maximum rightward and leftward ocular counterroll when the subject is tilted 20, 30 and 75° from the upright. Typical values for normal and L-D subjects do not overlap (Miller II & Graybiel 1963). The L-D subjects were thoroughly familiar with all aspects of the experiment except the dealing with centrifugation under water.

The subjects, 26 to 32 years of age, were in excellent health and performance had met the stringent medical requirements for duty involving flying. None had a history of middle ear disease. Routine hearing and caloric tests revealed no significant abnormality. Their counterrolling indices, obtained at 30-degree maximal tilt, ranged from 241 to 434. All were experienced in taking tests of many kinds, but none was familiar with the procedures in this experiment.

#### Apparatus

The heavy duty centrifuge (General Dynamics Astronautics (San Diego, Calif.)) was modified for our purpose. It was hydraulically driven, with adequate performance characteristics and excellent rotary coaxial connections. A gondola was fabricated that consisted of a cylindrical tank and observer's platform mounted in a trunnion 18.08 feet from the center of rotation (Fig. 1). It was equipped with a suitable water heater, closed circuit television, and voice communication system. By means of a pneumatic piston the whole assembly could be rotated about the trunnion pins through an arc of 45° in a period of 30 seconds with the centrifuge stationary or rotating. Inside the tank a metal seat was fitted to a rail system and could be removed, along with the subject, by means of a hoist. Bolted to the seat was the rear half of a Fiberglas body mold prepared for each subject; the front half was secured by "quick release" metal locks.

A visual test goggles (VTG) was devised which represented a modification of a visual target device used previously (Clark & Graybiel 1952). On the

TABLE 1 *Clinical findings in four deaf subjects with bilateral labyrinthine defects*

Subject	Age	Onset of meningitis, age	Cochlear function		Semicircular canal function <sup>b</sup>		Otolith function <sup>c</sup> body tilt	
			R	L	R	L	±50	±75
JO	36	7½	NI	NI	NI	NI	128	16
MY	26	8	NI	NI	NI	+ at 60 sec	63	82
PE	35	12	NI	NI	NI	NI	21	30
ZA	23	3½	+ >	+ >	NI	NI	14	36
			135 dB	130 dB				

Response to white = 1 sec up to 160 dB.

<sup>b</sup> Response to irrigation with water at 3 C±1 for 3 minutes.

Ocular counterrolling index. (See text.)

right side of the device a red Maddox lens illuminated by a collimated light shining through a pinhole aperture produced a line against a dark background the left side was an opaque eye covering. The lens could be rotated clockwise or counterclockwise about its center by means of a knurled knob. An external counter on the VTG displayed the meridional position of the target line to the nearest 0.1 which was relayed via a closed-circuit television system to the control room.

### Method

The subjects task described elsewhere in more detail (Graybiel & Clark 1965) consisted essentially in setting the target line, on demand to the horizontal of extrapersonal space. It should be noted that under all wet conditions, the subject's head was out of water and that he had to raise one hand above water to adjust the knob on the VTG. In other words, there was not total immersion. Under stationary conditions the experimenter offset (rotated) the target switched on the light, and the subject set it to the horizontal and signaled completion. The average of five such settings under prerotation conditions was used as the 'perceived horizontal' (PH) with which to compare subsequent settings. The centrifuge then was brought up to speeds causing a change in direction of the gravito-inertial horizontal (GIH) of 10, 20, or 30° in periods of never less than 20 seconds. The order of exposure involving the three changes in GIH was varied randomly among the eight subjects and among the five test sessions for any given subject. After constant rotation for at least an additional 20 seconds the target light was switched on and the subject was signalled to make the first of the five settings.

Five series of trials, either under "wet" or "dry" conditions, were con-

T 211 3 Perception of the oculogravic illusion in no wind and lake within and feeble subject  
Mean and standard deviation of five settings  
- Perceived horizontal.

Condition	Change in grain horizontal horizontal	Normal subject						Lake within and feeble subject					
		C1		D1		HU		L1°		JO		MY	
		f	s	f	s	f	s	f	s	f	s	f	s
Wet 117 Series 1	0	11		0.5		1.3		1.0		1.9		0.8	
	+10	2.8	2.8	10.1	1.9	+ 8.0	1.7	0.8	1.7	+ 1.9	1.3	+ 2.6	1.7
	+20	17.3	2.7	23.8	1.3	+19.3	1.7	0.3	4.7	+ 1.3	1.1	2.0	4.0
	+30	40.3	4.9	36.1	1.9	33.8	1.3	1.1	6.4	+ 2.7	1.6	+ 2.0	8.8
Wet 117 Series 11	0	11		0.9		0.5		0.7		0.8		1.3	
	+10	12.3	2.0	11.0	0.8	0.0	0.8	12.9	1.5	- 1.8	0.8	+ 2.1	2.8
	+20	20.8	1.6	31.1	0.8	30.8	1.5	14.8	1.8	- 2.8	0.9	+ 2.2	3.9
	+30	31.9	1.9	37.5	1.1	32.1	2.5	18.6	1.8	- 1.1	1.0	+ 2.5	1.8
Wet 118	0	2.8		0.9		1.0		1.1		0.0		1.7	
	+10	+19.7	8.5	+ 8.4	1.2	+ 8.8	0.6	+ 1.6	1.6	+ 3.5	2.0	+ 1.0	1.8
	+20	+20.3	4.8	20.1	0.9	+22.8	2.0	16.4	2.1	+ 2.6	1.9	+ 0.1	1.3
	+30	28.5	5.0	+37.2	0.5	+39.8	1.5	8.4	2.6	+ 6.8	1.5	+ 7.7	4.2
Dry Series 1	0	1.0		0.1		0.5		0.9		2.2		1.3	
	+10	+18.0	3.8	+12.7	1.0	+ 6.8	1.2	-21.5	0.8	1.1	1.3	+ 5.6	2.0
	+20	+25.3	2.8	+27.7	1.0	+18.9	1.5	-20.1	1.9	0.0	1.1	+ 0.9	0.3
	+30	+47.5	3.4	38.7	1.0	+33.5	2.1	10.5	1.8	+ 4.1	3.5	+11.7	1.5
Dry Series 11	0	0.7		1.2		0.1		3.1		1.1		2.0	
	+10	+11.2	2.1	11.1	1.1	+ 9.1	1.5	-10.8	2.5	+ 2.3	1.3	+ 1.0	2.8
	+20	34.3	1.8	25.1	0.8	+21.1	1.7	+10.1	2.9	8.7	1.0	+ 9.0	3.1
	+30	51.9	2.7	+37.9	0.7	+31.7	4.8	18.5	4.0	+12.7	1.5	+14.7	2.7

Subsequently dropped from the original series 1 and Fig 211.

ducted in the following order. In the first two the subjects wore bathing trunks and the tank was filled with water up to their necks; this was termed the water or "wet BT" condition. In the third and fourth series the subjects wore bathing trunks, and the tank was empty; this was referred to as 'dry' or "air" conditions. A fifth series under wet conditions, not originally contemplated, required the subjects to wear a foam rubber suit. This was termed the wet RS condition.

Manipulating the force environment is neither easy nor precise if comparison is made with manipulation of visual or auditory environments. In the present experiment the use of individually fitted molds ensured good positioning of the subject in the force environment under all conditions and excellent contact with his support under dry conditions.

## RESULTS AND DISCUSSION

The actual settings made by all subjects under all conditions in this experiment are shown in Table 2. Positive and negative values indicate respectively rotation of the target in the same and opposite direction to that of the gravito-inertial horizontal during positive accelerations.

It is seen in Table 2 that the settings of the normal subjects demonstrate a consistent and regular dependence on changes in the GIH in three but not in the fourth subject, LI. The bizarre settings in the case of LI were wholly unexpected, requiring individual consideration and necessitating his removal from the normal group.

In Fig. 2A is shown a comparison between the means of the settings made under dry and wet conditions by each normal subject. All subjects demonstrated an increasing tendency toward higher values in their settings for equivalent increases in change of direction of the GIH. This well known tendency has been termed the magnitude effect (Graybiel & Clark 1963) reflecting the progressively greater increase in magnitude compared with increasing angle of the gravito-inertial force vector: the positive acceleration of the curve depicting magnitude becoming substantial at 15° and rising rapidly after 30°. Only CU demonstrated significant differences between the settings made in dry and wet conditions. In the former he greatly overestimated the angular change in GIH at all three levels, while under wet conditions the overestimation was made only at 30° and the amount was moderate. Thus it would appear that water immersion reduces the magnitude of the oculogravic illusion by reducing nonotolith sensory inputs. Stated differently, nonotolith sensory inputs contributed significantly to the perception of the illusion by CU but not by DI or HU.

The bizarre settings in the case of LI are depicted in Fig. 2B. When questioned, he stated that he had experienced no difficulty in making the settings and considered his performance satisfactory.

The four L-D subjects manifested such great inter- and intra-individual

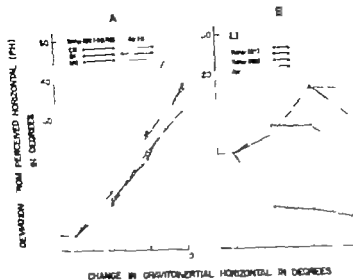


FIG. 2. Subjects estimates of the horizontal plotted against changes in the gravity inertial horizontal during centrifugation under dry and water immersion conditions. Subjects were exposed to change in direction of the force vector with reference to themselves in the frontal plane. They indicated the horizontal by rotating a line of light in darkness. (A) Settings made by three subjects constituting the normal group. Each point under wet conditions represents the mean of 15 settings in three experimental trials and under dry conditions the mean of 10 settings in two trials. (B) Atypical settings of one subject with normal vestibular functions as indicated by caloric tests and scale counterrolling.

variances that they are considered separately. The settings made by JO are depicted in Fig. 3A. The curves representing the values under wet BT conditions indicate that he did not perceive the illusion; hence there is no evidence using this indicator that he possesses residual otolith function. Under wet RS conditions the settings suggest that he may have perceived the oculogravic illusion. In the first series of trials under dry conditions the only evidence that JO may have perceived the illusion was the apparent magnitude effect at 30°. The curve representing the second series under dry conditions clearly indicates that JO perceived the illusion. Although this later curve shows values far below the expectation for normal subjects, its configuration is typical of one from a normal subject. Among our entire group of L.D. subjects (10) JO is one of two persons whose behavioral responses least resemble those of the normal, although he has the highest counterrolling index (Miller II & Graybiel, 1963).

The findings in the case of MY (Fig. 3B), clearly indicate that he perceived the illusion under dry but not wet BT conditions. His settings made under wet RS conditions are irregular but suggest that he may have perceived the illusion. These results show that otolith influence on the illusion was not

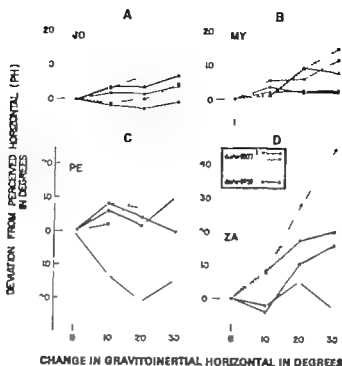


FIG 3 Estimates made by four deaf subjects with bilateral labyrinthine defects (L-D) Conditions the same as described for Fig 2. Each point represents the mean of five settings.

present but that there was evidence of influences from nonotolith sensory inputs under dry and possibly under wet RS conditions.

The settings made by PE, Fig 3 C, demonstrate that he readily perceived the illusion under dry conditions. When submerged PE stated that at times, he was confused and did not know which way was up. This was reflected in the greater variance in his settings than in those of the others. Under wet BT conditions the curve depicting his *first* series of trials indicates that the illusion may have been perceived minimally at 10 and 20 but not at 30 while in the *second* series his settings were discordant. In the wet RS series PE probably perceived the illusion at 10 and 30 but not at 20. These findings under wet conditions suggest a loss or reduction of nonotolith influences on perception of the illusion. The loss of "contact cues" caused disorientation which may have contributed to irregularities in his making the settings.

ZA's settings (Fig 3 D) under dry conditions show not only that he perceived the oculogravic illusion, but also, that his estimates were similar to those of the normal subject CU. Under wet BT conditions he perceived the illusion but considerably underestimated the change in angle in the gravito-inertial horizontal. Under wet RS conditions he did not perceive the illusion at 10 and 30 and whether he perceived it at 20 is doubtful. Among all of our L-D subjects, ZA's responses most nearly resemble the

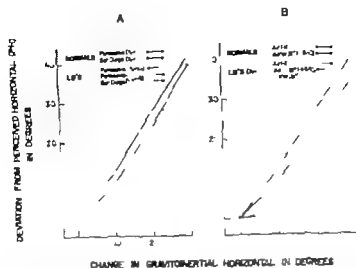


FIG. 4. (A) Comparisons between settings made under dry conditions in San Diego and Pensacola. Solid lines compare two normal groups composed of different subjects. The four L-D subjects participating at San Diego were part of the larger Pensacola group. (B) Comparison between mean settings made by normal and L-D subjects under wet and dry conditions.

normal. This similarity was not apparent initially when he was a participant in our other experiments but seems somehow to have been acquired as a result of practice. That he was the youngest among all the L-Ds at the time he acquired his vestibular defects (3 / years) may have been a factor.

In Fig. 4 A are the results of earlier experiments (Pensacola) which were similar in design to that of the dry series in the present study (San Diego). The curves drawn with solid lines compare the mean settings made by nine normal medical students with those made by the normal control subjects (three) used in this experiment, indicating that the latter are fairly representative of a larger group.

The dashed lines in Fig. 4 A represent settings made under dry conditions by the four L-D participants in this experiment and those made by the larger group of which they are a part. Comparison between means of the settings made by the entire group and by the group fragment on the previous occasion (Pensacola) indicates that the settings of the small group were substantially below those of the large group. When the settings made by the small L-D group in Pensacola are compared with those made by them in San Diego, higher values in the present study are seen except when the change in the GIH was 10.

Fig. 4 B summarizes all of the findings of the present experiment in terms of group differences between dry and wet conditions in the three normal and four L-D subjects.

## COMMENTS

In this experiment an attempt was made to control otolith and nonotolith sensory inputs which might influence the perceived direction of space as indicated by the apparent rotation of a line of light in the dark when the subject was exposed to a change in direction of the gravito-inertial horizontal with respect to himself. With regard to nonotolith receptors, stimulation was greatly reduced although not perfectly controlled by immersing the subjects in water up to the neck. Otolith inputs could only be controlled by selecting subjects with or without loss of otolith function; there was no possible way of reducing the effects of gravito-inertial forces on the field receptors in the vestibule. It is important to emphasize that in every experimental trial there was full opportunity for any influences having their origin in the otolith organs to become manifested, whereas there was not the same level of assurance that nonotolith inputs were completely excluded. Consequently the lowest values of the settings obtained in any series of trials under water immersion conditions still registered the maximal otolith influence. These lowest values for the three normal subjects were not far different from their values under dry conditions, with the exception of those of CU where the difference in magnitude under wet and dry conditions was greater than the magnitude of the illusion perceived under dry conditions by the L-D subjects JO and MY and not far below that for PE. Stated differently, the demonstration that nonotolith sensory inputs may or may not contribute to the perception of the oculogravic illusion in normal subjects explains, at least in part, individual variance in its perception among L-D subjects. To the extent that nonotolith contributions (to the illusion) can be demonstrated in normal subjects, they subtract from the need to invoke the phenomenon of compensation to account for the perception of the illusion in L-D subjects.

When the L-D subjects were exposed under water immersion conditions, any residual otolith receptors were inescapably stimulated while nonotolith receptor systems were never completely suppressed. Under these conditions the lowest values of the settings in the case of JO and MY indicate that they did not perceive the illusion and judged by this test there was not evidence of residual otolith function. The comparable "lowest values" in the case of PE and ZA indicate that they perceived an illusion but the likelihood that this was due to residual otolith function is small because the absolute values are small, inconstant, and far below the values under dry conditions.

At all events there is proof that nonotolith sensory inputs were mainly or entirely responsible for the perception of the illusion in L-D subjects and that the individual variance was great. For subject ZA the curves representing settings under dry conditions were similar to the values obtained with normal subjects. Under wet conditions the values were far lower than in the normal controls although still greater than those obtained from L-D subjects. The likelihood that these large nonotolith values in the case of



ZA would be matched by the nonotolith values of a normal subject would seem to be small based on our findings. It would require a setting of 70 when the force vector was at 30. This small likelihood is supported by the fact that, over the years, ZA has shown a strong tendency toward making higher estimates of the illusion.

The bizarre settings by LI under wet conditions seem to implicate neural connections between the otolith and visual pathways. The small differences between wet and dry conditions suggest that nonotolith sensory inputs were not previously involved. The ranks of the normal and L-D subjects within their groups with respect to their ocular counterrolling index did not have an apparent significance in terms of the perception of the illusion. Among the L-D subjects, JO had the highest value, an index of 176, yet the proof that he had lost all otolith function as determined by lack of perception of the illusion under immersion conditions, was good. Moreover as mentioned earlier among the entire group of L-D subjects he was one of two whose behavioral responses least resembled the normal. If the relatively large compensatory roll of the eyes in his case had its genesis in the otolith organs, then it measures a residuum of function with no easily demonstrable useful purpose.

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#### ZUSAMMENFASSUNG

Der getrennte und kombinierte Einfluss von Otolith- und Nichtotolithreizen auf die Wahrnehmung der oculogravischen Illusion wurde mittels Veränderung der inneren Umgebung und des gravit. inertialen Kraftfeldes untersucht. Die visuelle Raumwahrnehmung von 10er Marinesfliegern und vier tauben Personen mit beiderseitigen Labyrinthdefekten, wenn im Trockenen und in Wasser bis zum Nacken eingetaucht, wurde verglichen. Der Einfluss 1. der Kraftfeldrezeptoren in den Vestibularorganen und 2. der nichtvestibulären Propriozeptoren, die durch unseren Stützkontakt gereizt wurden, konnte untersucht werden. Es ergab sich hier den verschiedenen Bedingungen, dass für normale Personen der vestibuläre Anteil auf Grund der Richtung des grav. inertialen Kraftvektors orientierbar ist, dass jedoch der nichtvestibuläre Anteil wechselnd sein kann relativ gross oder klein sein. Personen mit beiderseitigen Labyrinthdefekten war ein nicht vestibulärer Anteil als vorhanden, allerdings aber stark individuell. Die Bedeutung der Befunde für das Testen der Funktion des Otolithorgan wird diskutiert.

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## DEVELOPMENT OF RESPIRATORY TRACT CILIA IN PETAL RABBITS

### *Electron Microscopic Investigation*

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Cilia develop in the respiratory tract of rabbits during the 22-23 days in utero. In the early "pre-cilia" stages, cuboidal cells elongate and develop microvilli on their upper or luminal surface. A large number of basal bodies are produced in the cytoplasm between the nucleus and upper surface. The basal bodies migrate towards the apical surface and orient themselves properly with respect to the surface. Finally a cilium rises above each basal body. Throughout the respiratory tract, this same sequence of steps is followed during cillogenesis, but the upper part of the airway develops its ciliated epithelium first. The nose is followed by the larynx, then the trachea and finally the bronchi.

We have been unable to locate a published comparison of the time course followed by various parts of the respiratory tract in the maturation of the ciliated epithelium, although the steps of cillogenesis in any single cell are well described. Motile cilia (sometimes called "kinocilia" to differentiate them from the non motile cilia of the inner ear known as "stereocilia") are each attached to a "basal body." Before the turn of the century anatomists discovered that basal bodies resembled centrioles and theorized that basal bodies were derived from centrioles. Lenhossek (1898) and Hennebury (1903) independently reported that basal bodies were produced within the cell from centriole division and that each cilium was formed by a basal body after it attached to the upper cell surface. Earlier Hennebury had showed that sperm's tail was similarly produced by a centriole. In 1910 Erhard described development of cilia and flagella in a number of protozoa, in a report with 146 citations from the literature. Details were added through the work of Ikeda (1908) in various human specimens, Helvestine (1931) in mussels, and by Renyi (1924). Saguchi (1917) wrote an interesting account of the history of the study of cilia which credited de Meide

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with the discovery of ciliary movement in 1683 and was a critique of the Henne-guy and Lenhossek theory. Leeson (1961) was the first to report use of the electron microscope to study ciliogenesis in the respiratory tract and his results confirmed the Henne-guy-Lenhossek concept. Better resolution provided by the electron microscope made it possible to show that each basal body is identical to a centriole in its fine structure. He was able to show that cilia did not begin to appear at the cells upper surface until the basal bodies had been produced deep within the cell and had migrated up to the upper surface. Microvilli were mentioned as a previous stage of cilia. Electron microscopic observations during the development of human nasal cilia were reported by Ewert (1965) in a comprehensive study of the function of cilia in the nose of healthy and diseased subjects. Regeneration of ciliated epithelium after trauma has been studied with light microscopy by A. C. Hilding (1965) and by Burian & Stockinger (1957 and 1963) and D. A. Hilding & A. C. Hilding (1966) with the aid of the electron microscope. The electron microscopic appearance of cilia at different phases during the beat cycle has been elegantly described by Satir (1963) and the details of each cilium by Rhodin (1966). Early electron microscopic studies of cilia were published by Brown (1945), Jakus & Hall (1946), Engstrom (1961) and Engstrom & Wersäll (1952).

The purpose of this paper is to add further details to the electron microscope description of ciliogenesis and to show the sequence of ciliary maturation in various areas of the respiratory tract of rabbits.

### MATERIALS AND METHODS

Rabbit fetuses were delivered by Caesarian section at 22-28 days after conception. Newborn and adult animals were used for comparison. As soon as possible after death, specimens were selected from the nose, larynx, trachea and bronchi and placed in cacodylate buffered 5% glutaraldehyde, then sub-divided into smaller pieces. After thorough washing in buffer the specimens were post fixed in buffered 1% osmium tetroxide, dehydrated and imbedded in Epon (Luft 1961). Sections were cut free hand with a

FIGS. 1-4. Illustrating the sequence of events which followed during maturation of ciliated epithelium. The process begins, and is completed. If the thickness of the cilia in the larynx, trachea and finally the bronchi. Phase-contrast light micrographs.

FIG. 1. Pre-cilia stage. The upper surface of each cell is domed and smooth, as seen with the light microscope. A goblet cell is present. Bronchial epithelium 22 days.

FIG. 2. First cilia appear. A goblet cell. The nasal epithelium passes this stage between 22 days, trachea by 25 days and the bronchial reaches it by 28 days. Laryngeal epithelium 22 days.

FIG. 3. Cilia well-developed. No goblet cell. Laryngeal epithelium at 25 days.

FIG. 4. Mature epithelium with goblet cell and cilia. Nasal epithelium, newborn.





FIG. 5 "Pre-cilia" stage. Laryngeal epithelium at 22 days. There are short microvilli on the upper surface of the stumpy columnar cells. There are a few dark cells (D) scattered through this two-layer epithelium that appear to be future goblet cells. Basement membrane (BM). Electron micrograph, 8500.

razor blade for phase-contrast light microscopy and with an L&B Ultratome for examination with an RCA EMU 3G electron microscope. A saturated solution of uranyl succinate in 50% alcohol was used to enhance contrast of sections.

## RESULTS

Cilia develop first in the upper part of the respiratory tract then appear at lower levels. As seen in Figs. 1-4 cilia were seen earliest in the nasal mucosa, then in the larynx, and finally in the trachea and bronchi. The first cilia were found in the nasal epithelium by the 22 day stage and the entire respiratory tract was ciliated by 28 days.

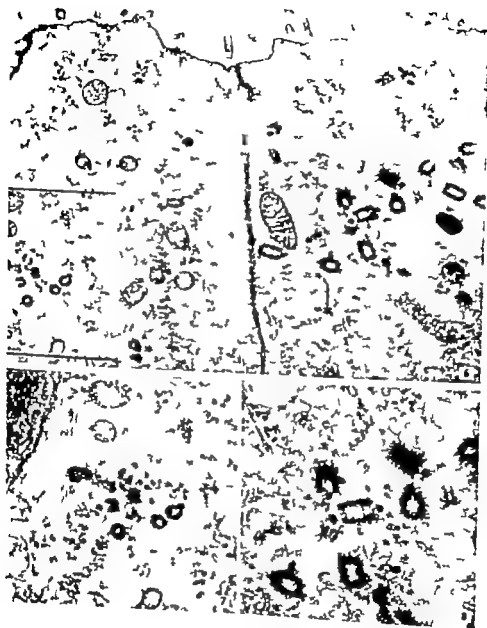


FIG. 6. "Pre-cilia" stage basal body formation. Nasal epithelium, 22 days. Cell on left shows a layer of small, faintly staining basal bodies during early step in their multiplication. Notice that each of the basal bodies in the cell on the right is accompanied by prominent dark "basal foot." Electron micrograph,  $\times 51,000$ .

FIG. 7 Higher magnification of marked area.  $\times 82,000$ .

FIG. 8 Higher magnification of marked area in Fig. 6  $\times 72,000$ .

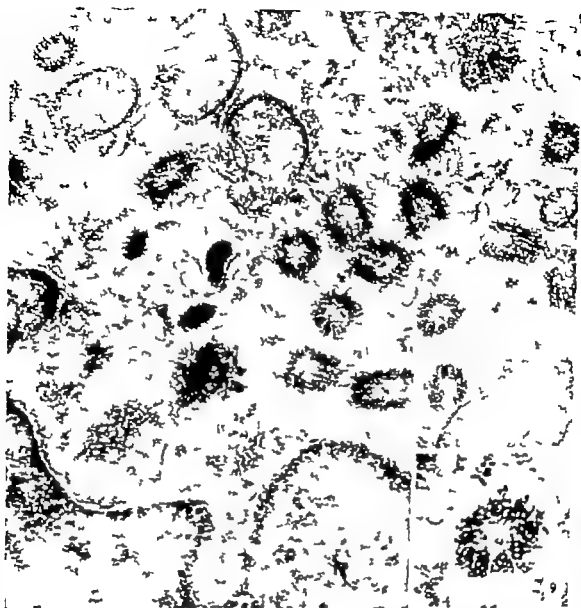


FIG. 9 Early stage of basal body formation near nucleus (V). Each basal body has triple microtubules.  $\times 185,000$ .

Identical stages were followed in the production of cilia by the cells from all locations although the process began and finished earlier at upper levels. Fig. 5 is a low power electron micrograph that illustrates the early "pre-cilia" stage. Two or more layers of cuboidal cells rest on a basement membrane. The upper or luminal surface is dome-shaped and covered by small microvilli. Occasional cells with dark nuclei and cytoplasm were found. They are probably the early stage of goblet cell formation.

The second stage of basal body production is illustrated in Figs. 6-8. Two neighboring cells show slightly different phases. On the left a few small hazy basal bodies have formed in a cluster. A pairing relationship seems to prevail. In the cell on the right the basal bodies have reached mature size and their details are more obvious. Often a black staining



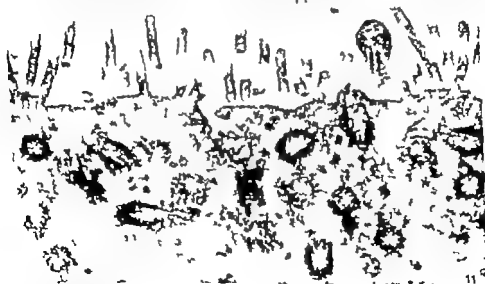


FIG. 10. Pre-cilia stage Bronchus, 25 days. A few cilia are beginning to push up through the pre-cilia cell surface. Electron micrograph,  $\times 5500$ .

FIG. 11. Higher magnification same specimen. There is no evidence that cilia are being formed from previously existing microvilli.



FIG. 12 Twenty-two day nasal epithelium. Cillogene is more abundant in the nose than elsewhere. 8400

FIG. 13 Solitary cilium in 22 day nasal mucous membrane (a) Most cells simultaneously produce many cilia but occasionally this unusual pattern is found in immature epithelium 10,300

FIG. 14 High magnification of solitary tubed cilium. The basal body is not apparent because of the plane of the section 112,000

sphere was found near the "end" of the basal body cylinder. In some cases it was attached near the side, with a resemblance to a "basal foot." It was tempting to wonder if these could be "buds" of future basal bodies and if this figure actually depicts basal body replication. The early basal bodies are formed near the nucleus (Fig. 9). Each consists of nine triple microtubules.

The next stage is the ascent of basal bodies through the cytoplasm to the upper surface orientation perpendicular to the surface, then beginning



FIG. 14. Laryngeal epithelium, 23 days. Some patches of cells are almost completely ciliated at this stage in the larynx. 9200.

FIG. 15. Higher magnification showing basal bodies clustered at top of cell with beginning formation of cilia. nail foot (F). Cross cut shafts above belong to another cell, when viewed through serial sections. 35,000.

growth of cilia (Figs. 10 and 11). Although not illustrated here the basal bodies ascend as a group. Often we found a zone free of basal bodies between the upper surface and the ascending group that gave us the impression that there may be a pause for proper alignment before the final move to the top. We have been unable to find a cilium forming within a microvillus and are now inclined to believe that cilia arise at the point of contact by the basal body with no particular reference to previously existing microvilli.

A single cilium can occasionally be found arising alone from a cell with only microvilli (Figs. 13 and 14). The illustrated example is a peculiar club-shaped cilium. It seems likely that this phenomenon is more closely related to the type of cilium formation that occurs elsewhere, for instance in the inner ear. Each cell facing endolymph, whether of the future stria vascularis, Reissner's membrane or organ of Corti, has a single kinocilium (Kikuchi & Hilding, 1966). Often these cells also have a number of microvilli.

Figures 14 and 15 illustrate the final stage of cillogenesis when most cells have mature-looking cilia, but a few are still in the process of producing cilia. The cells have become quite tall, and their mitochondria have become concentrated in their upper portion.

Mature ciliated cells have microvilli as well as cilia (Fig. 18). Micro-



FIG. 17 Early goblet cell (g) Ciliated cell (c) ppea mature Baseme 1 m mbrs (BM)  
Acta oto-laryng 65



FIG. 18. Adult ciliated epithelium from trachea showing bent cilia with basal bodies, several with "basal foot" (F). Macrofilii between filia are sometimes branched.

villi sometimes branch, and are often nearly as long as the cilia. Figure 19 is a composite which illustrates the major features of each cilium from its basal body and basal foot through its shaft to the tip.

We found a few dark cells (Figs. 5 and 17) scattered through the epithelium at every stage. Because their cytoplasm resembles that of goblet cells, we believe they represent a precursor stage.

#### DISCUSSION

Centrioles replicate themselves during cell division while they act in some mysterious way to help orient the strands of chromatin as they divide. During cillogenesis they reproduce themselves hundreds of times forming basal bodies, find their way to the upper cell surface, and then emit a pair of microtubules from each triplet of the basal body. They must have special protein synthesis mechanisms and contain substances fundamental to cell organization. They remain fascinating enigmas.

We had hoped that intensive study of the early stages of cillogenesis in the fetus would yield some clues about centriole replication. We found a few examples of early basal body formation, as seen in Figures 6 and 7 that suggested that they do increase in size after first appearing. Often

they occur in pairs and commonly are oriented at right angles to each other suggesting that new one emerges from the side of the parent

The large homogeneous cilia that are found in regeneration of ciliated epithelium after trauma are not present during ciliogenesis in utero. In other respects the two processes are identical.

The nucleus and cytoplasm of goblet cells is darker than that of ciliated cells. In immature epithelium scattered cells have the same kind of dark cytoplasm and nucleus and we believe can be identified as goblet cell precursors. We have found no evidence that ciliated cells can change into goblet cells.

It is the general experience of those who have used rabbits as experimental animals that they will survive if they are delivered by Caesarian section any time after the 28th day of gestation but that most will not survive if delivered earlier. It is tempting to suggest that ciliated epithelium is important for survival and its maturation must be completed in order for the young rabbit to survive. However we have no direct evidence that this concept is correct. We have learned that the respiratory tract epithelium of all levels has reached nearly its adult form by the 28th day of gestation.

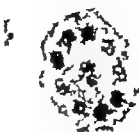
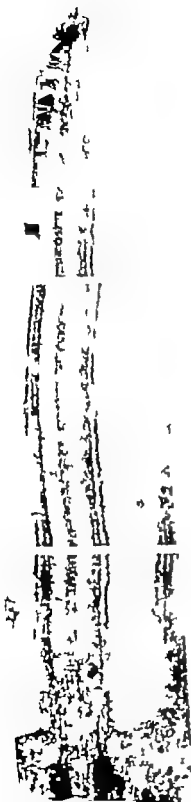
### ZUSAMMENFASSUNG

Cilien entwickeln sich in den Atemwegen von Kaninchen zwischen dem 22 und 28 Tag in utero. In den frühen präziliären Stadien findet man Elongation von kubischen Zellen und die Formierung von Mikrovilli an ihrer oberen der dem Lumen zugewandten Oberfläche. Eine grosse Anzahl von Basalkörperchen entwickelt sich im Cytoplasma zwischen dem Nukleus und der Oberfläche. Diese Basalkörperchen wandern gegen die apikale Oberfläche und orientieren sich zu ihr. Schliesslich entwickelt sich je ein Cilium über jedem Basalkörperchen. Während man die gleiche Folge von Entwicklungsschritten der Cillogenese in der ganzen Ausdehnung des Atemtraktes findet, entwickeln sich jedoch die Cilien in den oberen Abschnitten der Atemwege zuerst. Zuerst entwickeln sich Cilien in der Nase, dann folgt die Entwicklung im Kehlkopf, Trachea und schliesslich in den Bronchien.

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FIG. 19. Adult cilium as seen in longitudinal and cross-section (compound). Tip (T), Shaft (S), Origin (O) with nearby cross-cut microtubule, and basal body (B) with basal foot (F). Longitudinal section  $\times 12,000$  and cross-cut  $\times 138,000$ .



A<sup>T</sup>



S



B

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## ON THE INFLUENCE OF THE RETICULAR ACTIVATING SYSTEM UPON THE AUDITORY FUNCTION

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The aim of the present paper is to summarize the neurophysiological, neuropharmacological, and clinical evidence which indicate how the reticular formation of the brain influences the general processes of integration and particularly the auditory integration. The authors reach the conclusion that the ascending reticular tonic activity may influence the time constant of the sensory integration processes both through a modification of the overall conduction time of afferent impulses along the specific pathways and through a modification of the operation time of reflex mechanisms activated by the sensory input.

A great number of experimental and clinical findings show that there are two control mechanisms of the sensory input. The first type which might be defined as "specific" is formed by the so-called centrifugal or afferent sensory pathways, whereas the other "aspecific" type is represented by central nervous system (C.N.S.) levels not being an anatomical part of the different sensory pathways, but related to them by collateral branches.

Neuroanatomical and neurophysiological investigations have shown that there are at least six systems mutually interacting for the elaborations of sensory input (Livingston 1959) i.e. (a) ascending sensory pathways forming the classical lemnisci (b) ascending pathways connected with neurons of the reticular formation of the brain stem, which diffuse their impulses to the cortex (c) the ascending reticular projection, (d) pyramidal motor pathways, (e) extra-pyramidal motor pathways, (f) the brain-stem reticular formation with its ascending influences upon both the cerebral and cerebellar hemispheres, (g) the centrifugal sensory control mechanisms.

The dynamics of all these interdependent systems acting simultaneously has been defined as "transaction" thus indicating a more complex mechanism as compared with the rather elementary processes of "interaction".

Among these different systems, the brain-stem reticular formation plays an important role. The aim of the present paper is a review of the most important results obtained by animal experimentation concerning the reticular influence upon the auditory system. These data will be further related to some clinical findings.

### *Experimental Data*

The investigation of the reticular influence upon the auditory integration started when alterations of the auditory responses at the cortico-thalamic level were observed depending on the sleep-wakefulness state of the animal. Since these alterations of the auditory-evoked potential persist even if the stimulus parameters remain unchanged we might assume that they are related to the different functional condition of nervous structures of the thalamus and of the cerebral cortex in the sleep-wakefulness state, which is mainly regulated by the fluctuations of the tonic ascending reticular influence.

The main changes are well known when in an animal the EEG activity shows a transition from a sleep pattern to a pattern of moderate wakefulness, the cortico-thalamic potential evoked by an afferent impulse decreases in latency and waxing and waning of its recovery curve which is typical of the sleep condition disappears. This finding has been observed by King *et al* (1948) in the somesthetic cortex.

At the same time, when the EEG activity is "awakened" an increased amplitude of the response has been shown by Dumont & Dell (1958) and further by Bremer & Stoupe (1959).

Desmedt & La Grutta (1957) reported that when the EEG activity of an animal passes from a pattern of moderate arousal to one of maximal awakening, which might be compared in man to an intense emotional activation the cortical evoked response is clearly depressed.

In the cat, we have registered the potential evoked by a click in the medial geniculate and in the temporal cortical regions and we have been able to show that—during spontaneous transition from wakefulness to sleep—there is an increase of peak latency of the evoked response reaching 1-2 msec. During sleep the recovery curve of the geniculo-cortical excitability shows a typical waxing and waning with a period of about 150 msec; these oscillations disappear as soon as an arousal pattern occurs in the EEG record (Antonelli 1963).

These phenomena, in agreement with the data reported by King *et al* (1948) do not take place in the bulbar cochlear nuclei but are typical of the geniculo-cortical levels.

A number of neurophysiological and neuropharmacological controls indicate that these modifications depend upon the reticular tonic activity level. Actually we have found that electrical stimulation of the reticular formation brings back the latency values typical of the condition of awakening, whereas electrocoagulation of the reticular formation elicits the same (although quantitatively increased) variations of the auditory response which are characteristic of deep sleep. The peak latency of the response following reticular lesion increases by 2-3 msec (Antonelli, 1963a).

The same aspects of sleep that follow a reticular inactivation can be obtained by the use of drugs which at a certain dosage depress electively the reticular tonic activity as for instance barbiturates, while other CNS

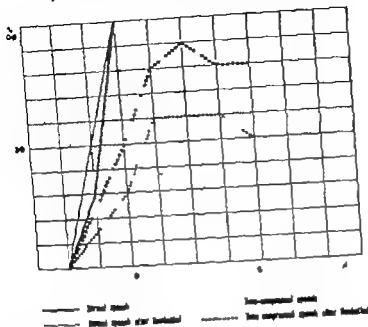


FIG. 1. Effect of single dose of Nembutal (100 mg) upon the reticulation curve for normal and time compressed speech (230 words/minute). Significant decrease of the discrimination score for time compressed speech only.

depressant drugs, such as chlorpromazine and meprobamate, have been shown to be inactive (Antonelli, 1963).

The specific ascending reticular influence upon the sensory integration has further been shown by experiments on the behaviour of unrestrained animals with chronically implanted electrodes. Fuster (1958) has shown that a slight electrical stimulation of the reticular formation leads to a marked improvement of the *la* histoscopic performances in the monkey.

The ascending reticular activity appears therefore to be capable of influencing the time constant of sensory integrative processes both through a shortening of the conduction time of afferent impulses along the specific pathways and through a modification of the operation time of reflex mechanisms activated by the sensory input.

#### Experiments in Man

When the threshold of succession between two clicks is measured in man during an EEG recording, a marked reduction of the threshold values may be observed when the task is performed in a state of desynchronized cortical activity (increased ascending reticular influence) as compared to a state of alpha activity (Antonelli, 1962).

In audiometric practice if the subject is presented with some lists of 1 word-redundancy sentences, it has been found that in a condition of normal sleepiness or after barbiturates administration (100 mg Nembutal) there

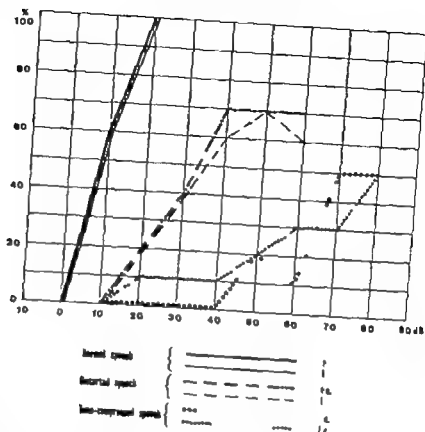


FIG. 2. Typical pattern of the sensitized speech tests performance in a case with nuclear reticular vestibular syndrome of the chronic type. Bilateral and severe loss of discrimination confined to the time-compressed speech discrimination.

exists a significant decrease of the intelligibility of time-compressed sentences as compared to data obtained by the same subject in a wakeful state (Albano & Antonelli 1963) (Fig. 1).

One might assume that this phenomenon derives from a slight obnubilation of mental conditions due to the sleepy state. However this doubt can be discarded as in our case the intelligibility deficit is present only for time-compressed speech whereas psycholeptic drugs, such as scopolamine and atropine, leading to a transitory mental obnubilation affect all low redundancy tests (time-compressed filtered interrupted speech tests) to a degree which is obviously proportional to their influence on mental factors (Calearo & Antonelli 1964).

On the other hand it is well known that in old age and in some diseases of the central nervous system such as Parkinson's disease there exists a particular impairment of discrimination for time-compressed speech. It has been found that in these subjects, if some psychoanaesthetic drugs are given which increase the reticular tonic activity there is a temporal improvement of time-compressed speech discrimination (Blondiau & Bocca, 1959; Antonelli & De Vitri unpublished data).

We know from vestibular pathology those cases where an acute or chronic condition of vertigo is accompanied by a very severe caloric hypo-

reflexia or areflexia. Some authors believe that the site of the lesion in such cases is situated in the central vestibular pathways (De Kleyn 1944) and more precisely in the bulbar vestibular nuclei and the surrounding reticular formation (Aralan, 1948 Aralan & Sala, 1956 Arslan, 1957)

In a number of these cases, a bilateral, symmetrical impairment of the discrimination for time-compressed speech has been found by Mosclaro & Pignataro (1964) (Fig. 2) This limited deficit (no other hearing alteration was present) appears to be directly related to the reticular vestibular alteration.

### CONCLUSIONS

Experimental data indicate that the function of cortico-thalamic structures checked by the activating reticular system may act on the sensory cortex, offering a mechanism which is able to influence the central elaboration of afferent impulses.

The experimental data in man and the audiometric findings in patients with nucleo-reticular syndromes confirm the existence of a reticular control of auditory integration and point to its diagnostic value.

We might deduce that a lesion of the brain stem reticular formation causes a decrease of the ability for temporal discrimination of auditory messages.

The deficit of discrimination for time-compressed speech in patients with bulbopontine reticular lesions might therefore offer an interesting clinical proof of the lesion of one of the mechanisms of auditory transaction

### ZUSAMMENFASSUNG

Zweck dieser Arbeit ist eine Zusammenfassung der neurophysiologischen, neuropharmakologischen und klinischen Befunde die dem Bew. in liefern, dass die Substantia reticularis des Hirnstamms die allgemeinen Integration vorgänge und insbesondere die Gehörintegration beeinflusst. Die Verfasser gehen zum Schluss, dass die ausserordentliche retikuläre tonische Aktivität die Zellkonstante der sensorischen Integrationsorgänge durch eine Veränderung der Übertragungszeit der afferenten Impulse längs d. spezifischen Bahnen sowie durch eine Veränderung der Zeit der reflektorische Mechanismen die durch die sensorielle Zufuhr aktiviert wird, beeinflusst.

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## ULTRASONIC CLEANER FOR OPERATING ROOM USE

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By means of a removable insert which may be sterilized, an ultrasonic cleaner for operating room use has been found practical. Used in connection with oto-surgery such as tympanoplasty and free-laying of the semicircular canals prior to ultrasonic irradiation, i.e., it cleans burrs, drills, curettes and other instruments from bone chips as well as coagulated blood.

A small, high intensity ultrasonic cleaning unit has found application in our operating room for the cleaning of drills, burrs, and curettes as well as other instruments used in connection with oto-surgery such as tympanoplasty, stapes surgery, free-laying of the semicircular canals prior to ultrasonic irradiation in the treatment of Menière's disease (Sjöberg *et al.* 1963) etc. Since the necessity of maintaining sterile conditions is at all times present, the instrument was designed to make this possible.

The basic unit employed is an ultrasonic cleaning unit of high intensity which was originally designed to solve the cleaning problems of the instrument and jewellery fields where the elimination of buffing and polishing compounds from intricate details is generally difficult and time consuming. For use in the operating room we have designed a special wide flanged trough (A) which may be sterilized and set down into the cleaning tank of the ultrasonic unit (B). Ultrasonic coupling is accomplished through a small amount of liquid in the bottom of the tank, the inserted trough having been designed to make contact at just the level which insures maximum effect.

The main requirement for good cleaning action is a high degree of ultrasonically induced cavitation in the bath. The term cavitation, as applied to ultrasonic treatment, has come to include the sequence of events from the formation of microscopic vapor phase bubbles during the negative pressure portion of the ultrasonic wave, to their collapse with rising pressure, and the resultant highly localized, but extremely intense, shock waves resulting from their collapse. It is mainly these shock waves which account for the ability of ultrasonic cleaning baths to eliminate contamination and embedded particles from crevices and hollows as well as smooth surfaces. Although the most effective cleaning is done with the combination of

The instrument discussed is available through Ultrapoint, P.O. 312, Uppsala, Sweden.

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## ZUSAMMENFASSUNG

Ein Ultraschallgerät mit sterilisierbarem Einsatz wurde erfolgreich zur keimfreien Reinigung von chirurgischen Instrumenten angewandt. In der Ohrenchirurgie z. B. bei Tympanoplastik oder bei Freilegung der Bogengänge für Ultraschallbestrahlung, können Schleifschiben, Bohrer und Kürett n auf einfache Weise an Knochensplittern und koaguliertem Blut gereinigt werden.

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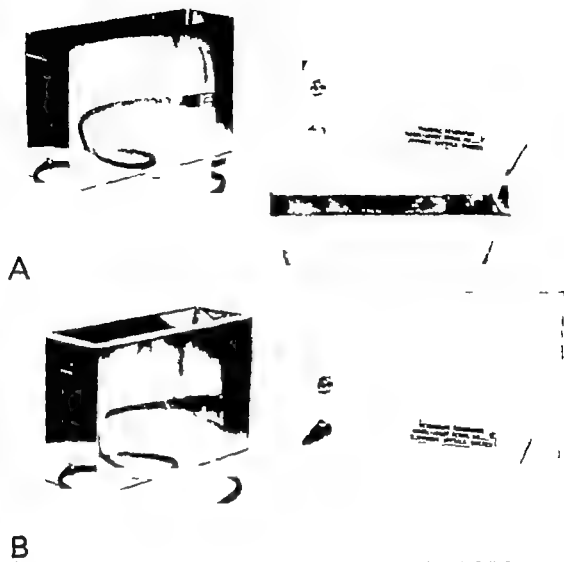


FIG. 1 The ultrasonic cleaner showing removal trough (A) inserted in cleaning tank (B)

ultrasound and a cleaning agent or solution specifically suited to the kind of deposit to be removed the need for any instrument in the operating room to be ready for immediate reuse during an operation that is to say sterile as well as clean, precluded the use of any special cleaning agents. Instead the ultrasonic bath has been made up of physiological saline solution—which incidentally is always at hand in the operating room.

The instrument itself consists of a transistorized generator delivering 40 watts of electrical energy at 32 kHz to a sandwich type aluminum barium titanate-aluminum transducer bonded to the bottom of a rectangular trough approximately  $60 \times 200 \times 50$  mm. Automatic tuning and a fixed output level eliminate all need for any adjustment during use. Thus, any nurse or operating room assistant can use the instrument without previous special training.

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## NOBEL SYMPOSIUM X

# Disorders of the Skull Base Region

Stockholm, August 13-16, 1968

### Tuesday August 13

18.00-20.00 Registration

19.30-21.00 Reception

### Wednesday August 14

Morning session

Professor T. Sjöstrand, Dean of the Medical  
Faculty of the Karolinska Institute

Professor C. A. Hamberger

Welcome and opening address

### ACOUSTIC NEUROMA I

Moderator: Jørgensen, L. B. W.

Oliverstone, H. Introduction

Engström, H. Anatomy of the vestibular nerve

Grpe, A. Normal anatomy of the cerebello-  
pontine angle as studied radiologically

Asch, G. Diagnosis of vestibular system  
disorders

Discussion

Coffee

Klein, J. Audiologic diagnosis of acoustic  
neuroma

Andersen, H. Intracranial reflexes in retro-  
cochlear lesions

Gritz, T. Roentgenological diagnosis in acous-  
tic neuroma

Bruus, S. Tomography: acoustic neuroma  
diagnosis

Lind, S. Liquor diagnosis in cases of  
acoustic neuroma

Moberg, A. Histopathology of the acoustic  
nerve

Glasscock, M. E. Endarterectomy of the ca-  
rotid artery within the temporal bone -

Movie

Discussion

Moderator's summary

Lunch

### Wednesday August 14

Afternoon session

### ACOUSTIC NEUROMA II

Moderator: Nørén, G.

Hause, W., Transient bone microsurgical  
removal of acoustic neuromas I

Hiltebeitel, W., Transient bone microsurgical  
removal of acoustic neuromas II

Hause, W., Hiltebeitel, W., Transient bone  
microsurgical removal of acoustic  
neuromas - Movie

Coffee

Lundberg, V. Result of total and subtotal  
removal of acoustic neuromas

Fleck, U. Surgical anatomy of the so-called  
internal auditory artery

Fluhr, E. Exploration of internal auditory  
meatus in acoustic neuroma

Discussion

Moderator's summary

### Thursday August 15

Morning session

### PITUITARY FUNCTION AND

### PITUITARY SURGERY

Moderator: Bateman, G.

Werdel, J. Anatomy of the pituitary gland

Hammer, G. and Rådberg, C. Roentgeno-  
logical anatomy of the sphenoidal sinus

Luft, R., Surgical endocrinology of the pi-  
tuitary

Angell-Jones, J. Transphenoidal approach  
to the pituitary

Luft, R., Pituitary ablation in diabetes mellitus

Discussion

Coffee

Burian, K., Transphenoidal hypophysec-  
tomy - Movie

*Escher F* Remission in dependence of the hormonal elimination in hypophysectomy of breast cancer

*Miller T* Hypophysectomy in mammary carcinomas

*Moberger G* Pharyngeal hypophysis following hypophysectomy

Discussion

Moderator's summary

Lunch

#### Thursday August 15

Afternoon session

##### PITUITARY TUMOURS

Moderator *Riskaer V*

*Laurén T* Sella turcica in pituitary tumours

*Widgermark J* Pituitary tumour pathology

*Sjögren B* Pituitary ablation in acromegaly

*Backlund E O* Stereotaxic treatment of craniopharyngiomas

*Aralan M* Ultrasonic hypophysectomy – Movie

Discussion

Coffee

*Voller G* Stereotaxic implantation of radioactive isotopes in the pituitary

*Sjögren B* Postoperative treatment of the hypophysectomized patient

Discussion

Moderator's summary

#### Friday August 16

Morning session

##### GLOMUS JUGULARE TUMOURS

Moderator *Portimann M*

*Bordley J* Introduction

*Hamberger B* Catecholamines in glomus jugulare tumours

*Laurén T* Angiography in diagnosis of glomus jugulare tumours

*Gefrot T* Syndrome jugulare

*Franén S* Needle biopsy in skull base tumours

*Gefrot T Hamberger C A Laurén T Werstål J* Diagnosis and treatment of glomus jugulare tumours – Movie

Coffee

*House W* Operative treatment of glomus jugulare tumours

*House W* Operation of glomus jugulare tumours – Movie

Discussion

Moderator's summary

Lunch

#### Friday August 16

Afternoon session

##### MISCELLANEOUS SKULL BASE TUMOURS

Moderator *Vielhake A*

*Fluur B* Clinical aspects of parapharyngeal tumours

*Enderoth C M.* Histological aspects of parapharyngeal tumours

*Zehm S* The surgical approach to the external part of the base of the skull related to the anterior and medial cranial fossa

*Berdal P* Carotid body tumours

*Ketcham A* Advanced carcinoma of the ethmoid

Discussion

Coffee

##### TRAUMA OF THE BASE OF THE SKULL

Moderator *Diamant H*

*Escher F* Classification and treatment of liquorrhea in skull base fractures

*Hertlin L* Neurosurgical aspects of liquorrhea

*Wersall J* Transphenoidal approach to the skull base in treatment of liquorrhea

Discussion

Moderator's summary

*Gustafsson B* Closing address

#### Saturday August 17

Practical demonstration of audiological methods in otoneurological diagnosis will be demonstrated in the Audiology Department Karolinska Sjukhuset

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Svenska kliniska prövningar (unde publ.) på cirka 500 patienter har visat en mycket god effekt och låga biverkningsfrekvenser. Med en dosering av 1 tablett 3 gånger dagligen vid de flesta patienterna besvärslösa. Sparsamt gynnsamma behandlingsresultat notades vid allergiska rinit samt rekurrerande rinit och otoskleros. Ett stort antal patienter stod kontinuerligt på Rinomar under 1-1½ års tid med oförminskad effektivitet. Hos dessa patienter återkom vid försök till utsättning besvärerna för att åter försvinnade vid fortsatt medförföring. Som särskilt värdefullt i samband att Rinomar utan att störa sömnen gav patienterna besvärslöshet under natten.

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### INDIKATIONER

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	Prophylaxis	200 mg t.i.d.	From no observable effect to 3% protection
	Prophylaxis	400 mg b.i.d.	From 41% to 67% protection
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Varicella (chicken pox)	Prophylaxis	500 mg t.i.d.	No observable effect
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Varicella (chicken pox)	Therapy (suppression)	500 mg t.i.d.	No observable effect
Poliomyelitis	Therapy (suppression)	5 mg b.i.d.	No observable effect
Varicella (chicken pox)	Therapy (suppression)	500 mg t.i.d.	No observable effect

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(1) Kottorf, B. 1937-1938 års influensaepidemi i Sverige. Sv. Läkartidn. 27 (1938), p. 911

(2) Flumidin — samlade erfarenheter med ABOB, AB Kabi, Stockholm 1961, p. 8 (50 pages, partially in English, available upon request from AB Kabi, Stockholm 3).

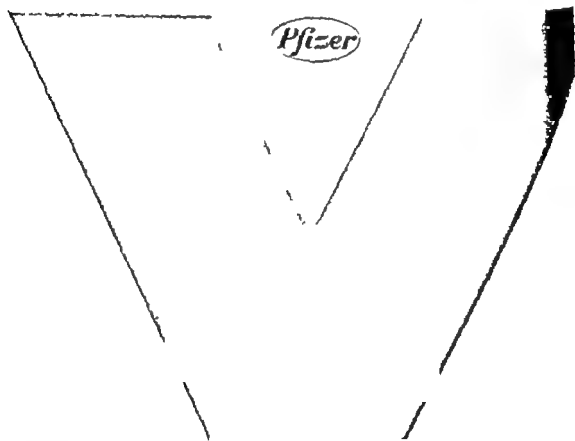
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